AGREEMENT OF THE MEMBER STATE COMMITTEE

ON THE IDENTIFICATION OF

(±)-1,7,7-trimethyl-3-[(4-methylphenyl)methylene]bicyclo[2.2.1]heptan-2-one covering any of the individual isomers and/or combinations thereof (4-MBC)

AS SUBSTANCES OF VERY HIGH CONCERN

under Articles 57 and 59 of Regulation (EC) 1907/2006

Adopted on 29 November 2021

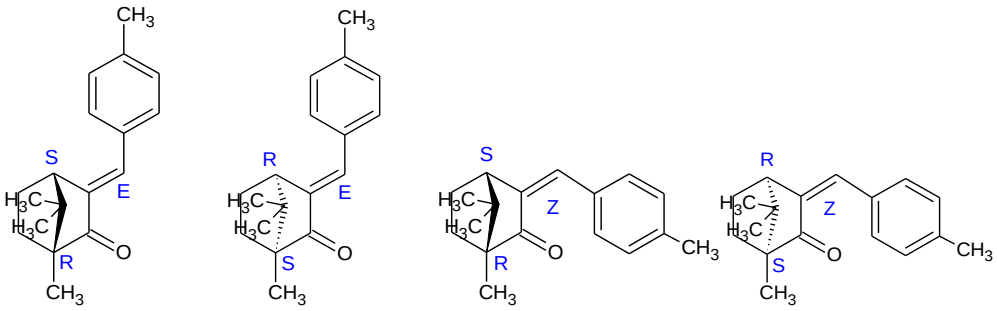
This agreement concerns

(±)-1,7,7-trimethyl-3-[(4-methylphenyl)methylene]bicyclo[2.2.1]heptan-2-one covering any of the individual isomers and/or combinations thereof (4-MBC)

EC number: -

CAS number: -

Structural formulae of the possible isomers:



The Member State Committee agreed that:

1. **(±)-1,7,7-trimethyl-3-[(4-methylphenyl)methylene]bicyclo[2.2.1]heptan-2-one covering any of the individual isomers and/or combinations thereof (4-MBC) are substances under Article 57 (f) of Regulation (EC) 1907/2006 (REACH) because they are substances with endocrine disrupting properties for which there is scientific evidence of probable serious effects to human health which gives rise to an equivalent level of concern to substances listed under Article 57 (a) to (e) of REACH.**

2. **4-MBC must be added to the Candidate list of substances of very high concern**.

Annex 1: Scientific evidence of probable serious effects to human health which gives rise to an equivalent level of concern to substances listed in points (a) to (e) of Article 57 REACH

The information below is based on Draft Support Document (Member State Committee, 29 November 2021)

(±)-1,7,7-trimethyl-3-[(4-methylphenyl)methylene]bicyclo[2.2.1]heptan-2-one covering any of the individual isomers and/or combinations thereof (commonly referred to as 4-methylbenzylidene camphor or **4-MBC**) are identified as substances of very high concern in accordance with Article 57(f) of Regulation (EC) 1907/2006 (REACH) because of their endocrine disrupting properties for which there is scientific evidence of probable serious effects to human health which gives rise to an equivalent level of concern to those substances listed in points (a) to (e) of Article 57 REACH. This proposal is made based on the available evidence for 4-MBC. Due to the structural similarity between the different isomers and in the absence of evidence on the individual isomers, it has to be assumed that all individual isomers and/or combinations thereof have endocrine disrupting properties.

Endocrine disrupting (ED) properties of 4-MBC relevant for human health:

Thyroid mode of action

There is some evidence of thyroid-related (**T**) endocrine activity based on the few available *in vitro* studies and strong evidence in a larger number of *in vivo* studies showing a consistent pattern of increased thyroid stimulating hormone (**TSH**) and tri-iodothyronine (**T3**). There is also strong evidence for adverse effect on the thyroid gland in several *in vivo* studies (e.g. increased weight and altered histopathological findings). According to the Mode of Action analysis (**MoA**), there is strong evidence that the adverse effects on the thyroid gland are plausibly linked to the thyroid disrupting endocrine activity seen *in vitro* and *in vivo*. According to the ECHA/EFSA ED guidance (ECHA/EFSA 2018), such effects are considered relevant for human health and could pose a hazard to humans, in particular if alterations of thyroid hormones should occur during the critical windows of pre- and postnatal neurological development. Such adverse health effects on offspring neurodevelopment are often irreversible and can have consequences later in life. Neurodevelopment has not been sufficiently investigated with 4-MBC, and therefore such effects cannot be excluded. Irrespective of the identified knowledge gaps related to neurodevelopment, the consistently seen adverse effects on thyroid gland weight and histopathology clearly show that 4-MBC is a thyroid hormone system disrupting chemical.

Estrogenic mode of action

There is strong evidence for endocrine activity related to estrogen receptor (**ER**) activation. The available *in vitro* assays provide strong evidence for induction of estrogenic response in the E-screen and for ER agonism. *In vivo*, several mechanistic studies show altered growth of estrogen sensitive tissues, including increased uterus weight in uterotrophic assays and altered expression of estrogen-regulated genes in several target tissues, confirming the strong evidence of an estrogenic activity.

In female rodents, there is moderate to strong scientific evidence that combined perinatal and adult exposure to 4-MBC can lead to adverse effects on sexual behaviour (reduced proceptive and receptive behaviour, and increased rejection behaviour towards the male) as well as a moderate degree of evidence for other adverse effects on female reproductive development (changes in ovary weight, uterine weight and ano-genital distance (**AGD**), vaginal opening (**VO**)). In addition, there is weak-moderate evidence of alterations in circulating follicle stimulating hormone (**FSH**), luteinising hormone (**LH**) and gonadotropin releasing hormone (**GnRH**) levels *in vivo*. The performed MoA analysis shows a biologically plausible link between the estrogenic endocrine mechanism and the reported adverse effects. The molecular initiating event is activation of the ER(s), which can result in increased ER activity in specific tissues, including specific areas of the brain. If such changes occur during the first two weeks of postnatal life, the female brain is not organised properly. This can lead to disrupted regulation of LH and FSH in adulthood and may as a consequence adversely affect sexual behaviour. Additionally, altered ER signalling has been shown in some studies to alter female AGD, ovary and uterus development and timing of sexual maturation.

In male rodents, there is moderate to strong scientific evidence of persistent reductions in prostate weight in several studies in adult animals, whereas the results are less clear from the available developmental toxicity studies. The Mode of action analysis shows that estrogens are important regulators of adult prostate growth and function and that increased ER signalling may affect prostate growth during early prostate development. Although patterns of effects of estrogenic substances may vary, it is biologically plausible that the observed effects of 4-MBC are related to increase in estrogen signalling. In addition to the role of estrogens, it has been shown that dysregulation of the FSH system plays a significant role in prostate growth. Although the evidence is currently limited, it is biologically plausible that altered gonadotropin secretion may contribute to the observed changes in adult prostate growth.

Other potential modes of action
In addition, there is some supportive *in vitro* evidence showing androgen receptor (**AR**) antagonistic activity. This endocrine activity could also plausibly contribute to the adverse effects on both the male and female reproductive system in rodents.

Summary of the ED assessment
Therefore, there is scientific evidence to conclude that 4-MBC are endocrine disruptors via T and E modalities, according to a mode of action analysis including an evaluation of biological plausibility.

Equivalent level of concern

- 4-MBC exposure has been shown to consistently disrupt the thyroid hormone system and consequently cause adverse effects on the thyroid gland. Thyroid hormone system disruption can have potentially serious and irreversible effects on humans, in particular on neurodevelopment. This can impact the quality of life and raises societal concern of a high and increasing burden. A number of vulnerable populations may be particularly susceptible to thyroid hormone (**TH**) disruption

induced by 4-MBC. Pregnancy is likely to be a period of sensitivity to the alteration of TH regulation, with potential consequences for neurodevelopment of the offspring.

- The observed adverse reproductive effects in male and female rodents have been plausibly linked to the estrogenic mode of action, shown both *in vitro* and *in vivo* after 4-MBC exposure. These, and potentially other adverse effects in humans, caused by endocrine disruption via the E modality are considered serious, as similar effects in humans could cause sub- and infertility. For humans, sub- and infertility is not only detrimental to the propagation of the species, but it also has a major impact on quality of life. Additionally, fertility treatment and counselling carry high societal costs.

Based on the available studies, it may be difficult to establish a safe level of 4-MBC. Mixture effects, where substances act additively or with synergistic effects, cannot be excluded and this might impact the threshold of toxicity. Moreover, the difficulty to establish a safe level with sufficient certainty raises concern particularly on the capacity to manage safe use of the substances for sensitive populations. Establishing safe levels for these particularly sensitive populations is surrounded with large uncertainties, and alterations of thyroid hormones during the critical windows of pre- and post-natal neurological development may have consequences later in life. The complexity of the response in reaction to thyroid disturbance is not fully characterised and understood, and considering the range of functions influenced by THs, it is also highly challenging to fully characterise these effects in experimental studies.

Altogether, this gives rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 REACH.

Conclusion

Overall, it is concluded that the substances ***(±)-1,7,7-trimethyl-3-[(4-methylphenyl) methylene]bicyclo[2.2.1]heptan-2-one*** covering any of the individual isomers and/or combinations thereof *(4-methylbenzylidene camphor, 4-MBC)* meet the criteria of Article 57(f) of REACH, due to their endocrine disrupting properties for which there is scientific evidence of probable serious effects to human health which give rise to an equivalent level of concern to those for other substances listed in paragraphs (a) to (e) of Article 57 of REACH Regulation.

Annex 2: Procedure

1. On 27 August 2021, Denmark presented a proposal under Article 59(3) and Annex XV of the REACH Regulation on identification of 4-MBC as substances which satisfy the criteria of Article 57 (f) REACH.
2. On 3 September 2021, the Annex XV dossier was circulated to Member States and the Annex XV report was made available to interested parties on the ECHA website as required by Articles 59(3) and 59(4).
3. 4-MBC received comments from both Member States and interested parties on the proposal.
4. On 17 November 2021, the dossier was referred to the Member State Committee (MSC) and agreed in the written procedure of the MSC with closing date of 29 November 2021.