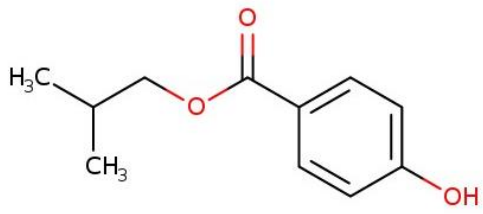
AGREEMENT OF THE MEMBER STATE COMMITTEE
ON THE IDENTIFICATION OF

Isobutyl 4-hydroxybenzoate

AS A SUBSTANCE OF VERY HIGH CONCERN
under Articles 57 and 59 of Regulation (EC) 1907/2006
Adopted on 28 November 2022

This agreement concerns
Isobutyl 4-hydroxybenzoate
EC number: 224-208-8
CAS number: 4247-02-3
Molecular formula: $C_{11}H_{14}0_3$
Structural formula:



The Member State Committee agreed that:

1. **Isobutyl 4-hydroxybenzoate is a substance under Article 57 (f) of Regulation (EC) 1907/2006 (REACH) because it is a substance 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. **Isobutyl 4-hydroxybenzoate must be added to the Candidate list of substances of very high concern**.

Annex 1: Scientific evidence for identification of a substance of very high concern

The information below is based on Support Document (Member State Committee, 28 November 2022)

Isobutyl 4-hydroxybenzoate (IBP) is identified as a substance of very high concern (SVHC) in accordance with Article 57(f) of Regulation (EC) 1907/2006 (REACH) because of its 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 of other substances listed in points (a) to (e) of Article 57 of the REACH Regulation.

Endocrine disrupting (ED) properties of IBP relevant for human health:

Estrogenic activity
There is strong evidence that IBP affects estrogen receptor (ER) binding and transactivation and estrogen dependent signalling in target cells *in vitro*. *In vivo,* there is moderate-strong evidence of estrogenic activity as evidenced in uterotrophic assays, showing increased uterine weight and altered expression of estrogen-regulated genes and proteins.

Adverse effects
There is low-moderate evidence of adverse effects on ovary and uterus histopathology after pubertal IBP exposure, due to lack of studies and limited study reliability. There are no reliable studies for IBP investigating adverse effects on sperm quality in perinatally exposed rats.

Therefore, a read across approach is applied from the source substance butylparaben (BP) to the target substance IBP. BP has already been identified as a SVHC because of its endocrine disrupting properties to human health. The read-across is supported by the structural similarity of the substances and by similar estrogenic activity and potency observed *in vitro* and *in vivo*.

A number of rodent studies using oral gavage or subcutaneous exposure show moderate-strong evidence for adverse effects of BP on sperm count and quality, after perinatal exposure. No effect on endocrine related endpoints (sperm parameters and anogenital distance) are seen in a recent developmental dietary exposure study, using continuous breeding protocol. However, the adverse findings observed in other studies should not be neglected. These inconsistencies can be considered to reflect differences in bioavailability using different study designs such as exposure routes and periods. Hence, after consideration of all available *in vivo* results for BP, there is still moderate-strong evidence that developmental exposure to BP, and consequently to IBP, can cause adverse effects on sperm count and quality.

Plausible link between adverse effects and endocrine activity:

The mode of action (MoA) analysis leads to the conclusion that IBP acts via an estrogenic MoA. Since limited information was available for IBP on adverse effects, information on BP was included in the MoA analysis (perinatal exposure). The molecular initiating event is activation of the ER(s). In developing males, increased ER signaling results in altered testicular development and subsequently altered testicular function in adulthood. In turn, reduced sperm count and quality are observed. The analysis led to the conclusion that it is biologically plausible that ER activation during development leads to the observed adverse effects on the male reproductive system following perinatal exposure to IBP.

Summary of the ED assessment
There is scientific evidence to conclude that IBP is an endocrine disruptor via the estrogen modality, according to a MoA analysis including an evaluation of biological plausibility.

Equivalent level of concern:

The adverse effects on BP are reduced sperm count and quality as observed in rodent studies using perinatal exposure. Effects are irreversible and are shown to occur later in life after exposure in the perinatal period only. These effects are considered severe as similar effects in humans could cause sub- and infertility. Sub- and infertility is not only detrimental to the propagation of the species, but also has a major impact on quality of life. Fertility treatment and counselling carries high societal costs.

No safe concentration/level can be derived from the available data on adverse reproductive effects via an endocrine MoA. Two of the available studies show reduced sperm count or quality in perinatally exposed rats at the lowest tested dose and therefore no no-observed-effect-level can be determined for this endpoint. 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. Moreover, mixture effects, where substances act additively or with synergistic effects, cannot be excluded and this might impact the threshold of toxicity.

Altogether, IBP exposure gives rise to an equivalent level of concern to substances listed in Article 57 points (a) to (e) due to its endocrine disrupting properties for human health. Notably, the conclusion is reached using a read-across approach with BP as a source substance – a substance already identified as a SVHC because of its endocrine disrupting properties to human health.

In conclusion:

Overall, it is concluded that the substance isobutyl 4-hydroxybenzoate meets the criteria of 57(f) of Regulation (EC) 1907/2006 (REACH) because of its 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 of the REACH Regulation.

Annex 2: Procedure

1. On 26 August 2022, Denmark presented a proposal under Article 59(3) and Annex XV of the REACH Regulation on identification of isobutyl 4-hydroxybenzoate as a substance which satisfy the criteria of Article 57(f) of REACH.
2. On 2 September 2022, 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. Isobutyl 4-hydroxybenzoate received comments from both Member States and interested parties on the proposal.
4. On 16 November 2022, the dossier was referred to the Member State Committee (MSC) and agreed in the written procedure of the MSC with closing date of 28 November 2022.