General comment:

The association European Chemistry for Textile and Leather (EUCTL) represents companies producing and putting on the market chemicals for the textiles and leather value chains in Europe. The EUCTL membership covers more than 70% of chemicals for textiles and leather produced in Europe, including Switzerland.

EUCTL wants to comment the CLH intention on bisphenol F as this substance occurs as impurity in synthetic leather retanning agents and less important in synthetic aftertreatment agents for polyamide dyeing processes to increase color fastness.

EUCTL ask ECHA to thoroughly assess the CLH proposal as EUCTL thinks that some inaccurate conclusions were made by the dossier submitter and insufficient evidence was provided for its reasoning.

Comments on the open hazard classes Reproductive toxicity:

The CLH report on Bisphenol F (BPF = 4,4'-methylenediphenol, CAS 620-92-8, dated 22-6-2023) concludes in a proposal for harmonised classification and labelling that „based on a weight of evidence assessment including read-across from bisphenol A (BPA) that BPF fulfils the criteria as reproductive toxicant category 1B (Repr. 1B, H360F) as it exhibits adverse effects on male and female sexual function and fertility in the absence of marked general toxicity.

As no REACH registration exists for BPF, the CLH intention is mainly based on literature data and read-across to BPA. The used studies are rated according to Klimisch criteria. One study was rated Klimisch 1, the others are rated Klimisch 2 and 3.

It is obvious that in comparison with BPA the data on BPF is rather limited and there exists in particular no one or two generation toxicity study to fully assess fertility and developmental toxicity for the test substance.

The available information on reproductive toxicity following BPF exposure, gathered from scientific studies in the open literature, seems not sufficiently robust to conclude on clear evidence for adverse effects on sexual function and fertility since in vivo and in vitro data altogether only give some indication of BPF reproductive toxicity.

Below, some selected studies were described to exemplify the limitation of the data base.

Page 38: In the CLH assessment much weight was given to a 48-week oral repeated toxicity study in male rats (Ullah et al 2018 b) in which several findings suggest a substance related effect on the male reproductive organs:
At the top dose level (50 µg/L) a small but significant decrease in gonadosomatic index (-7%), relative epididymis (- 4 %) relative seminal vesicle weight (-7%) were reported. Effect on relative prostate weight, absolute seminal vesicle weight, absolute prostate weight and absolute paired testis weight were not statistically different from control animals. The authors of the study conclude that „ these results *suggest* that exposure … for chronic duration can induce structural changes in testicular tissue". The study did not include

treatment of female rats or a mating procedure. Moreover, the study was classified by ECHA as unreliable.

Page 45 + 75: Very recently a reproduction/developmental toxicity screening test with BPF according to OECD TG 421 has been reported by Lee et al.,2022 (Klimisch: Reliable without restriction). The study covered a broad dose range, (Dose levels: 1, 5, 20 and 100 mg/kg bodyweight, dissolved in 4ml/kg of corn oil. Exposure: Oral gavage, daily for 2 weeks prior to mating and throughout the day before sacrifice in males (total 62days) and through lactation day (LD) 13 in females (total at least 41 days).
No significant BPF-related changes were observed in the male rats. A decrease in bodyweight and food consumption was observed in the female rats treated with BPF at 20 and 100 mg/kg/day. Ovarian weight decrease was reported, and number of implantation sites were decreased at 100 mg / kg/day. Based on the results of this study, the no-observed-adverse-effect levels (NOAELs) of BPF for general systemic and reproductive effects were 5 and 20 mg/kg/day, respectively. Thus, no specific reprotoxic effects were seen with BPF below a general systemic toxic effect.

Page 36: In a 28-day study (Higashihara at al. 2007; reliable with restriction) no relevant reproductive toxic effects and no histopathological effects could be determined.

This should be kept in mind when effects on fertility are interpreted in other studies where dose levels were chosen that are above a general toxicity level.

In vivo studies on sexual function and fertility following BPA and BPF exposure were presented in the CLH report to underline a read across argumentation.
Most comparative in vivo study however have significant shortcomings due to the fact that they were judged as Klimisch not reliable, not assignable or reliable with restriction, which limit a meaningful comparison.
In addition, studies which may describe a reprotoxic effect are contradictory. For example, in one study it is reported that the testosterone levels decreased in another study the levels increased. Moreover, in some of the studies describing a reprotoxic effect solvents like ethanol, acetone or DMSO are used to dissolve BPF. These solvents themselves may cause reproduction toxicity at a certain level.

Despite the similar structure between these substances and some similarity in physicochemical properties, significant differences between the two substances have not been fully acknowledged in the CLH report:

1) Significant differences in the metabolic detoxification exist between the two substances. Whereas BPF is mainly metabolized in rats to the BPF-sulfate (> 50%) the main metabolite of BPA is a BPA-glucuronide.

2) The comparative toxicokinetic study by Gingerich (2019) reports on a series of maternal and foetal kinetic data after subcutaneous injection of BPF and BPA:

   At comparable dose levels c_{max} plasma levels in female sheep and in foetus were significantly lower for BPF. Total body substance clearance for BPF in females was more than two times higher than for BPA. Similarly, the AUC for maternal and foetal

data show that the values for BPF were about only 50 % of the values for BPA. The authors concluded on toxicokinetic differences among the bisphenols and that toxicokinetic differences call for a more careful approach when extrapolating kinetic information from one bisphenol chemical to another.

3) The summary table of a study by Castellini et al (2021, effects of Bisphenol S (BPS) and BPF on human spermatozoa: an in vitro study in the CLH is somewhat misleading, documenting a „trend“ of adverse effects on sperm motility, sperm viability and sperm mitochondrial function. This is in contrast to the authors summary: „In conclusion, BPS and BPF seem to be safer alternatives to BPA for sperm biology, as they do not affect mitochondrial functions, sperm motility and viability. “