Response to the ECHA Public Consultation on the CLH report "Proposal for Harmonized Classification and Labelling of Acetaldehyde" based on regulation (EC) 1272/2008 (CLP Regulation), Annex VI, Part 2.

The European Flavour Association (EFFA) wishes to submit the following comments regarding the classification proposals for mutagenicity (Muta. 1B) and carcinogenicity (Carc. 1B) for acetaldehyde (AA).

For the reasons indicated below, we do not believe there is sufficient evidence to support the proposed re-classification of acetaldehyde as a Category 1B carcinogen, and therefore suggest that the current classification Category 2 carcinogen be maintained. Furthermore, while there may be evidence to support a Muta. 2 classification to address mutagenicity in somatic cells, we are convinced that the available data on the mutagenicity in germ cells is not sufficient to support a Muta. 1B classification.

In the first instance, we wish to remind that this proposal relates to a substance listed in Annex VI, Table 3.1 of the CLP Regulation with the following harmonized classification: H224 (Flam. Liq. 1); H319 (Eye Irrit. 2); H335 (STOT SE 3); H351 (Carc. 2). This harmonized classification in Regulation EC 1272/2008 is actually a straight translation, i.e. without any modification, from the DSD to the CLP classification scheme of the classification R12 (F+); R40 (Carc. Cat.3); R36/37 (Xi) (See Annex VI, Table 3.2 of the CLP Regulation). The latter is the harmonized classification that was introduced in Annex I of the Directive 67/548/EEC via the Commission Directive 93/72/EEC of 1 September 1993, i.e. the 19th ATP (Adaptation to Technical Progress).

Therefore, it makes sense that a classification determined in 1993 is revisited in view of any additional (test) data that meanwhile may have become available.

The CLH report covers additional information that is mostly related to in vitro mutagenicity studies in mammalian cells, including human cells, and in vivo animal mutagenicity studies. Overall, EFFA agrees that a number of studies provide some indication for AA being mutagenic to somatic cells. But there are basically only two studies related to animal germ cell mutagenicity listed: the first one (Lähdetie 1988) was already available when the initial harmonized classification was established in 1993, whereas the second one is a more recent study (Madrigal-Bujaidar et al. 2002). Whilst the Lähdetie 1988 study showed no effect on germ cells, the latter study suggests positive effects.

However, the data in the study by Madrigal-Bujaidar et al (2002) were obtained by intra-peritoneal injection which is not an appropriate route of exposure and does not reflect normal intake in relation to humans. This "non-physiological route of exposure" is also acknowledged by the authors of the CLH-dossier (page 39). Furthermore, the authors of the study did not find a dose-dependent effect. EFFA also wishes to highlight the fact that the biological relevance of the study type, i.e. Sister Chromatid Exchanges (SCE), has been put into question, which has led to the deletion of the respective OECD guideline for the in vitro SCE assay in 2014. Overall, this calls for a critical review of these test data that are also in contradiction to the study by Lähdetie (1988).

Despite the authors of the CLH report stating "…. *there is limited evidence that acetaldehyde is genotoxic (sister chromatid exchanges) in germ cells of mice (Madrigal-Bujaidar et al. 2002), when the substance was given by intraperitoneal injection"* (page 39) and *" in another animal study no abnormal sperm cells, and no meiotic micronuclei in spermatids were observed at dose levels inducing acute toxicity (Lähdetie 1988)"*, they conclude on page 40: "*based on the available data, it is recommended to classify acetaldehyde as a germ cell mutagen in category 1 B, "substance to be regarded as if they induce heritable mutations in the germ cells of humans".*

The assumption that AA will reach the germ cells in humans is not based on hard experimental facts and therefore we do not support the above conclusion from the CLH authors. Yet, we acknowledge there are reports with positive in vitro genotoxicity data on somatic cells (albeit much of the positive data are from non-standard tests) and also some positive effects on somatic cells in animals (although in most cases these are also from intra-peritoneal injections). To account for these reports, we rather suggest an alternative classification in Category 2 "Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans".

In contrast to mutagenicity, there is limited new data present regarding carcinogenicity compared to the studies available for the harmonized classification in 1993, namely a study by Soffritti et al. (2002) and a study by Homann et al. (1997), both being questioned for their reliability (page 41 of the CLH-dossier).

The CLH report confirms that no human studies addressing the carcinogenicity of acetaldehyde on its own have been retrieved from public literature, hence acknowledging that the human data on carcinogenicity are not sufficient to derive a classification (page 49).

This means that the body of evidence regarding carcinogenicity of acetaldehyde essentially consists of the studies that basically provided for the initial harmonized "DSD" classification as Carcinogenicity Category 3 according to the Dangerous Substance Directive, which was translated to Carcinogenicity Category 2 according to the CLP regulation: "suspected human carcinogen".

Hence, we therefore strongly question the proposal to move acetaldehyde in category Carc. 1B and recommend to keep Carc. 2 as reflected in the current harmonized CLP classification.

In summary EFFA recommends to maintain the current classification for acetaldehyde with regard to carcinogenicity, i.e. Category 2, bearing the hazard statement H351 (suspected of causing cancer). On the other hand, we acknowledge that new data on mutagenicity may warrant a classification for this hazard class with Category 2, H341 (suspected of causing genetic defects). However, we disagree with the authors' conclusion that a classification for germ cell mutagenicity as Category 1B is justified.

REFERENCES

Homann N. et al. Effects of acetaldehyde on cell regeneration and differentiation of the upper gastrointestinal tract mucosa. J. Natl. Cancer Inst. 1997;89 (22):1692-1697

Lähdetie J. Effects of vinyl acetate and acetaldehyde on sperm morphology and meiotic micronuclei in mice. Mutat Res. 1988;202:171-178
Madrigal-Bujaidar E; et al. Effect of disulfiram on the genotoxic potential of acetaldehyde in mouse spermatogonial cells. Teratog Carcinog Mutagen. 2002;22(2):83-91
Soffritti M. et al. Results of long-term experimental studies on the carcinogenicity of formaldehyde and acetaldehyde in rats. Ann N Y Acad Sci. 2002;982:87-105