January 24th, 2019

To

Environment Agency Austria
Spittelauer Lände 5
A-1090 Vienna

Re: **Comments on Harmonized Classification and Labelling (CLH) proposal report for 4-methylpentan-2-one (MIBK), EC Number: 203-550-1, CAS Number: 108-10-1, Annex VI Index Number: 606-004-00-4.**

On behalf of the Methyl Isobutyl Ketone (MIBK) REACH Consortium we would like to submit comments on MIBK in response to the call for public consultation on the proposed changes for CLP Annex VI Index number 606-004-00-4.

While the MIBK REACH consortium supports the Environment Agency Austria's CLH proposal for classifying MIBK as STOT-RE category 3 (H336) for narcotic effects, it respectfully disagrees with the CLH proposal for classifying MIBK for Carcinogenicity Category 2. According to the Environment Agency Austria. The Environment Agency Austria recognized that the MIBK-induced liver tumors were CAR-mediated and the male rat kidney tumors were α2u-globulin mediated. However, they concluded that the evidence is not sufficient to exclude human relevance. This is contradictory to ECHA's position. ECHA has accepted the alpha-2u-globulin MOA as well as the CAR/PXR MOA for other chemicals that act through one, or both of these MOAs and concluded that kidney effects associated with alpha-2u-globulin nephropathy and male rat renal tumors are not relevant for human health risk assessment and classification in its evaluation for other chemicals like carvone, dodecane and tetrahydrofuran (ECHA, 2013, ECHA 2018a, ECHA 2018b). Also, according to both the International Agency for Research on Cancer (IARC) and the U.S. Environmental Protection Agency (US EPA), chemically induced renal neoplasms in male rats, developed coincident with α2u-globulin nephropathy, are not considered predictive of risk to humans (IARC 1999 Consensus report; Swenberg and Lehman-McKeeman1999; US EPA 1991). The observed MIBK-induced liver effects are analogous to phenobarbital (PB)-induced effects, with CAR/PXR activation as the common initiating event leading to mouse liver tumors (Hughes et al 2016). In addition, several papers using known CAR/PXR activators such as PB (Elcombe 2014; Yamada et al 2014, Friedman GD, et al. 2009; IARC 2001; La Vecchia al. 2014; Lake BG. 2009) have demonstrated CAR/PXR activation is not mitogenic to the human liver, using human hepatocytes in chimeric mice and epidemiological studies of human populations chronically exposed to PB.

Altogether, there is a strong weight-of-evidence (WOE) in peer-reviewed literature that is supportive of a CAR-mediated activation in rodents that has limited, if any, relevance to humans. Accordingly, we propose Environment Agency Austria reconsider the addition of Carcinogen Category 2 (H351) classification to MIBK due to the lack of human relevance

Note: The Environment Agency Austria refers to the protein α2**u**-globulin as α2**μ**-globulin which is a different protein that is not in the scope of the current document. For consistency and accuracy, the consortium will refer to it as α2u-globulin.

Arkema France.

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