COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

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Substance name: tetrafluoroethylene
CAS number: 116-14-3
EC number: 204-126-9
Dossier submitter: Ireland

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
14.03.2019	United Kingdom	Fluoromonomers and Related Substances REACH Consortium (FMC): TFE Subgroup	Industry or trade association	1
Comment received				
The self-classification for TFE adopted by the members of the FMC TFE Subgroup and reflected in the Joint Submission IUCLID dossier is as follows: Flam. Gas 1 - H220: Extremely flammable gas. Compressed gas - H280: Contains gas under pressure; may explode if heated. Carc. 1B - H350: May cause cancer by inhalation. STOT SE 2 - H371: May cause damage to the kidney by inhalation. Whilst the proposed harmonised classification is focused on the carcinogenic potential, this self-classification embraces all of the known hazards of TFE, which are of critical importance during its normal handling and use. The members of the FMC TFE Subgroup would encourage ECHA to harmonise the classification and labelling of TFE for all four hazards.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	France		MemberState	2
Comment received				
Study in rats: - It should be specified that the increase of combined renal adenoma and carcinoma is mostly driven by adenoma rather than carcinoma. - It is noted that mononuclear cell leukaemia has a high spontaneous tumour incidence in F344 rats (CLP guidance page 382); therefore, the comparison with historical control data is particularly useful for this type of tumours. In addition, the fact that this tumour occurs without a dose-response relationship in both males and females decreases the biological				

relevance of this finding.

- The same comment also applies to the interstitial cell adenoma observed in male rats. In particular, it is noted that the incidence in the concurrent control is higher than the historical control. Therefore, the biological relevance of this finding is unclear.

Overall interpretation:

Some types of tumours observed are not associated with a clear dose-response relationship. A very low rate of survival (< 5%) is noted in the highest tested group in male rats, in the mid and high doses in male mice and in all groups in female mice. In general, a carcinogenicity study should be stopped when the mortality exceeds 25%. Therefore, the results in these groups should be interpreted in the light of this high mortality. However, the consistency of the effects between sexes and/or species and their incidence higher than historical controls support their biological relevance. Overall, FR agrees with the proposed classification based on the multiple tumours occurring in different species and/or sexes.

Date	Country	Organisation	Type of Organisation	Comment number
21.03.2019	Finland		MemberState	3
Comment received				
The studies available include standard guideline carcinogenicity studies (inhalation route) in mice and rats and a cohort mortality study on workers exposed to tetrafluoroethylene at production sites. In both male and female mice statistically significant increases were detected in the incidences of hepatocellular carcinomas, hepatic haemangiosarcomas and histiocytic sarcomas (all organs). In rats, statistically increased incidences of renal tubule adenomas, hepatocellular carci-nomas in both sexes were noted. In female rats, incidences of mononuclear cell leukemias were elevated. The observed neoplasms in rodents are relevant for humans. In a cohort mortality study (Consonni et al., 2013), increased standard mortality ratios (SMRs) for liver, oesophageal and pancreatic cancers and leukemias were observed. The SMRs have large confidence intervals weakening the reliability of the estimates. Moreover, other limita-tions and confounding factors in exposure assessment of this study were indicated in the report. Taken together, the evidence from two animal species demonstrate a causal relationship between exposure of tetrafluoroethylene and increased incidences of neoplasms. Therefore, classification in category 2, which according to CLP is based on limited evidence of carcinogenicity in animal studies, is not warranted. Regarding information on humans, data is available only on one study with limited evidence. The suggested classification of tetrafluoroethylene as category 1B carcinogen is supported.				

Date	Country	Organisation	Type of Organisation	Comment number
14.03.2019	United Kingdom	Fluoromonomers and Related Substances REACH Consortium (FMC): TFE Subgroup	Industry or trade association	4
Comment received				

The members of the FMC TFE Subgroup agree with the proposal to classify TFE as a Carcinogen Cat 1B H350.

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In the paragraph "Relevance of the information for human carcinogenicity", the following statement is made.

"The available human data, while limited, demonstrated an increase in SMR for cancers of the same organs observed in the animal studies and thus can be used as supporting evidence".

This statement places undue emphasis on the significance of the findings of the epidemiological study which has a number of limitations, all which are adequately described in the preceding paragraphs. Of particular note are the large confidence intervals associated with these SMRs leading to uncertainty about their reliability. On strict scientific grounds, the epidemiological data provide no support for the classification proposal.

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It is argued that, based on the available data, it is not possible to conclusively prove that cancer is caused only by the inhalation route of exposure and that, as a consequence, the specification of the route of exposure is not warranted. The members of the FMC TFE Subgroup disagree with this opinion on pragmatic grounds, given the physico-chemical properties of TFE, and propose that the inhalation route should be specified when citing H350.