Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

Tetrafluoroethylene

EC Number: 204-126-9
CAS Number: 116-14-3

CLH-O-0000006727-64-01/F

Adopted

5 December 2019

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: tetrafluoroethylene
EC number: 204-126-9
CAS number: 116-14-3
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.

Dossier Submitter's Response

The IE CA would like to thank the FMC TFE Subgroup for their comment. We acknowledge the self-classification adopted by the members of the subgroup. However, the scope of the current proposal is limited to the harmonised classification and labelling of the carcinogenicity endpoint in accordance with Article 36(1) of CLP.

RAC's response

Noted.

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.

Dossier Submitter's Response

The IE CA would like to thank the FR CA for their comments and support.
Please find below our responses to the specific observations made.

- We agree with the observation that the increase of combined renal tubule adenoma or carcinoma observed in the rat was mostly driven by the increased incidence of renal adenomas. This is reflected in the conclusion drawn for this tumour type in section 10.9.1 of the CLH report: *"The dose dependent increase in renal tubule adenomas observed in this study is considered treatment related"*. For information we include below the incidences of renal tubule adenomas and carcinomas observed in rats which are also reported in table 13 in the CLH report."

	Males				**Females**			
Dose group (ppm)	**0**	**156**	**312**	**625**	**0**	**312**	**625**	**1250**
Number of animals examined	**50**	**50**	**50**	**50**	**50**	**50**	**50**	**50**
Kidney								
Single and Step Sections:								
Renal tubule adenoma	2	4	9*	13**	0	3	3	8**
Renal tubule carcinoma	1	1	2	0	0	0	0	3
Renal tubule adenoma or carcinoma	3	5	9	13**	0	3	3	10*

- We agree that comparison of mononuclear cell leukaemia with historical control data is useful given the high spontaneous incidence of this lesion in the tested species and the absence of a dose-response relationship. Comparison with historical control data is made in Section 10.9.1 of the CLH report: *"the incidence of this lesion in control males (68 %) exceeded the range observed in male historical control data from 2-year NTP inhalation studies for all types of leukaemia (34 % - 66) and therefore the significance of the increase in low dose males is unclear. However, the incidence in control females was within the range observed in female historical control data from 2-year NTP inhalation studies (30 % - 54 %) and therefore it cannot be excluded that the statistically significant increase in the incidence of this lesion in low and high dose females is related to tetrafluoroethylene exposure."*

  The historical control data for this lesion is reported in Table 14 in Section 10.9.1 of the CLH report. For clarity, we have summarised the incidence of mononuclear cell leukaemia observed in the study and the historical control range for this lesion in the following table:

Mononuclear cell leukaemia	0 ppm	156 ppm	312 ppm	625 ppm	Historical control mean ± SD	Historical control range
Male percentage incidence	68%	86%	76%	62%	54.4% ± 8.8%	34 - 66%
Female percentage incidence	32%	62%	46%	72%	40.1% ± 7.2%	30 - 54%

  It cannot be excluded that the increased incidence of mononuclear cell leukaemia in females compared with both concurrent and historical control data is related to tetrafluoroethylene exposure. Therefore we consider that this is supporting evidence in our overall conclusion that tetrafluoroethylene meets the criteria for Carc. 1B classification.

- We agree that the biological relevance of the increased incidence of interstitial cell adenomas is unclear. It is stated in section 10.9.1 of the CLH report that a significant increase in interstitial cell adenomas in the testes was observed in males of the mid and high dose when compared with both the concurrent control and historical control males in NTP 2-year inhalation studies. The CLH report concludes that *"It is noted that this type of tumour is common in aging F334/N rats and therefore the biological significance of the increase in exposed males is unclear."*

  The historical control data for this lesion is reported in Table 14 in Section 10.9.1 of the CLH report. For clarity, we have summarised the incidence of interstitial cell adenoma observed in the study and the historical control range for this lesion in the following table:

Testes: Interstitial cell adenoma	0 ppm	156 ppm	312 ppm	625 ppm	Historical control mean ± SD	Historical control range
Male percentage incidence	78%	80%	96%	94%	68.7% ± 8.7%	54% - 83%

We acknowledge the low survival rates observed in the available carcinogenicity studies. However, we have interpreted the data in light of the observed mortality and conclude that there are biologically relevant and statistically significant increases in the incidence of multiple tumour types in both sexes of two species, demonstrating a causal relationship between tetrafluoroethylene exposure and increased incidence of neoplasms.

RAC's response
RAC agrees with the interpretation of the DS.

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 carcinomas 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.
Dossier Submitter's Response
The IE CA would like to thank the FI CA for their comments and support.
RAC's response
Noted.

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. Page 28. 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.

Dossier Submitter's Response

We would like to thank the FMC TFE Subgroup for their support.

- We agree that the epidemiological study is of limited reliability due to the deficiencies noted, including large confidence intervals, confounding factors and low statistical power. We therefore conclude in Section 10.9.1 of the CLH report that *"a direct correlation between worker exposure to tetrafluoroethylene and the development of cancer cannot be made"*. This study is included as supporting information and as stated in Section 10.9.2, is not sufficient to demonstrate a causal relationship between human exposure and the development of cancer.

- We acknowledge that inhalation is the most likely route of exposure given the physicochemical properties of tetrafluoroethylene. However, table 3.6.3 of Annex I of CLP states that the route of exposure is stated only where "it is conclusively proven that no other routes of exposure cause the hazard". We note that the available carcinogenicity studies were conducted via whole body inhalation and therefore it cannot be excluded that some oral or dermal exposure to the test material occurred. In addition there is currently no data which conclusively proves that other routes of exposure do not cause carcinogenicity. Consequently, we consider that it cannot be conclusively proven that no other routes of exposure cause the hazard. Therefore, we propose not to include the inhalation route when specifying H350 as suggested.

RAC's response

The CLH report carefully reflects the issues. The epidemiological data are not critical for the classification category, the positive tendency at target organs can be seen as supportive in general.