Committee for Risk Assessment

RAC

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

5 December 2019

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OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **Tetrafluoroethylene**

EC Number: **204-126-9**

CAS Number: **116-14-3**

The proposal was submitted by **Ireland** and received by RAC on **29 November 2018.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Ireland has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **21 January 2019**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **22 March 2019**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Agnes Schulte**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **5 December 2019** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal	TBD	tetrafluoroethylene	204-126-9	116-14-3	Carc. 1B	H350	GHS08	H350			
RAC opinion	TBD	tetrafluoroethylene	204-126-9	116-14-3	Carc. 1B	H350	GHS08	H350			
Resulting Annex VI entry if agreed by COM	TBD	tetrafluoroethylene	204-126-9	116-14-3	Carc. 1B	H350	GHS08	H350			

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

There is no harmonised classification and labelling for tetrafluoroethylene (TFE) and it was not previously discussed by the Technical Committee for Classification and Labelling under Directive 67/548/EEC. TFE has been classified by several expert committees including the National Toxicology Programme (NTP, 1997) and the International Agency for Research on Cancer (IARC, 2016). However, RAC notes that more than two thirds of notifiers to the classification and labelling inventory do not self-classify TFE for carcinogenicity.

TFE is a halogenated olefin that occurs as a colourless, odourless gas at room temperature. It is practically insoluble in water. TFE is used primarily as a monomer in the industrial production of polymers. TFE is very flammable and at high pressures it may polymerize easily without a stabiliser, especially if heated or in the presence of oxygen (IARC, 1979; NTP, 1997). Because of its instability, *d*-limonene is added as a stabiliser and it requires tight control when handling. Registrants under the REACH Regulation report that it is transferred to on-site polymerisation units by direct pipeline at EU manufacturing sites.

RAC notes that impurities are not addressed in the CLH report. According to IARC (2016), industrial-grade TFE generally has a purity of > 99.7 % and TFE for making fluoropolymers usually contains only 1 to 10 ppm (w/w) as impurities (ECETOC, 2003). However, NTP (1997) reported that during 2-year studies, gas chromatography indicated peaks for perfluorocyclobutane (the most abundant dimer produced during TFE decomposition) and *d*-limonene with areas less than or equal to 1.21 % and 0.56 % (respectively) relative to the major peak (TFE). In addition, trifluoroethylene, methylene fluoride, vinyl fluoride, and vinylidene fluoride were present at ≤ 1.7 ppm. None of these chemicals has a harmonised classification but RAC notes that some are self-classified as carcinogens or considered as such by IARC and/or NTP. However, considering their low concentrations in TFE and that *d*-limonene and perfluorocyclobutane are less volatile than TFE, minimising these chemicals in the exposure chambers, RAC does not consider impurities relevant for classification.

The DS included repeated dose toxicity, toxicokinetics and mutagenicity data as supporting information for the assessment of carcinogenicity but the scope of the proposal was limited to the carcinogenicity endpoint in accordance with Article 36(1) of CLP. RAC also considers the above available information useful for classifying substances for carcinogenicity.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

Overall information

The genotoxic data are used for information only whether a genotoxic mechanism of action is to be assumed for the induction of carcinogenic effects.

In vitro tests

TFE induces neither gene mutations in bacterial cells nor in a mammalian cell culture (CHO cells) with or without S9-mix. In a chromosomal aberration test no clastogenic effects are induced with or without S9-mix (CHO cells).

In vivo tests

Micronucleus tests (mice; inhalation) are negative in bone marrow cells as well as in peripheral blood samples.
The available UDS test (indicator test; mice; inhalation) shows no increase in unscheduled DNA synthesis.
Additional information is provided by a 2-year carcinogenicity study (mice; inhalation) regarding the involvement of H- and K-ras oncogenes in development of hepatic tumours. The mutation frequency of H- and K-ras oncogenes is not different to those of controls. Therefore liver tumours in mice may occur via a ras-independent pathway.

Summary

The Dossier Submitter (DS) concluded that tetrafluoroethylene is not genotoxic despite some limitations to the quality of the available data (none of the tests has been carried out according to the current OECD test guideline; the reproducibility of the test data is sometimes inadequate or incomplete in the publications.)
This conclusion is provided as supportive information for the carcinogenicity assessment only.

Comments received during public consultation

No comments were submitted during the public consultation.

Assessment and comparison with the classification criteria

Following tests for genotoxicity with TFE are available:

In vitro tests

- Bacterial gene mutation test (four tests): negative
- Mammalian cell gene mutation test (two tests; HPRT; CHO cells): negative
- Mammalian chromosome aberration test (CHO cells): negative

In vivo tests

- Mammalian erythrocyte micronucleus test (bone marrow cells): negative
- Mammalian erythrocyte micronucleus test (peripheral blood): negative
- Unscheduled DNA synthesis (DNA): negative

Additional information

- Involvement of the H- and K-ras oncogens in the development of hepatic tumours in mice as a part of a 2-year carcinogenicity study: negative

RAC follows the view of the dossier submitter that despite deficiencies regarding the data presentation and test quality the genotoxicity of TFE can be assessed.

A comparison of the genotoxic data with the classification criteria is not necessary because the DS has informed that the evaluation of these data is used for information only whether a genotoxic mechanism of action is to be assumed for the induction of carcinogenic effects.

Conclusion

Based on the available data RAC supports the conclusion of the DS that TFE does not induce genotoxic effects either *in vitro* or *in vivo* and therefore **does not warrant classification for germ cell mutagenicity**.

RAC evaluation of specific target organ toxicity – repeated exposure (STOT RE)

Summary of the Dossier Submitter's proposal

The DS provided information on repeated dose toxicity studies as supportive information (without comparison with CLP criteria).

Table 19 of the CLH report summarises the results from a number of inhalation repeated dose toxicity studies with TFE with exposure periods of between 14 and 90 days. In the 14- and 16-day studies in rats, increased kidney weights were observed in males from 312 ppm and females from 1 250 ppm and renal tubule degeneration in males from 625 ppm and females from 1 250 ppm. Liver weights were also increased in both sexes. In a 16-day study in mice, kidney weights were comparable with control. However, increased incidence of renal tubule epithelial cell karyomegaly, located in the inner renal cortex, was observed in males and females. Increased liver weights were reported in male rats and female mice from 5 000 ppm, but this was not accompanied by histopathological findings.

In a 90-day study in rats, an increase in kidney weight was reported in male rats from 1 250 ppm and female rats from 625 ppm. An increased incidence of renal tubule degeneration was observed in males from 625 ppm and in females from 2 500 ppm, with the same etiology as observed in the 16-day study. A concentration-dependent proteinuria was observed in all exposed males and in females from 2 500 ppm, which may be consistent with renal tubular degeneration. Alteration of haematocrit, haemoglobin and erythrocyte count was observed in males and females which the study authors characterised as a normocytic, normochromic and non-responsive anaemia. In a 90-day study in mice, polyuria was observed in males and females at 2 500 and 5 000 ppm. An increased incidence of karyomegaly of the renal tubule epithelial cells was observed in males and females from 1 250 ppm, with the same etiology as observed in the 16-day study. Similar to the 90-day rat study, a normocytic, normochromic and non-responsive anaemia was observed in both sexes. In a 90-day study in hamsters, no effects on kidney or liver were reported. An increased incidence of testicular atrophy was observed in males at 1 989 ppm.

RAC evaluation of carcinogenicity

Summary of the Dossier Submitter's proposal

Human data

A cohort mortality study examined the cancer risk in workers exposed to TFE at six polytetrafluoroethylene production sites across Europe and the USA from 1950 to 2002 (Consonni et. al., 2013). All sites handled TFE and ammonium pentadecafluorooctanoate (APFO). No exposure monitoring data were available. Instead, the exposure assessment was undertaken using a job-exposure matrix based on yearly semi quantitative estimates of TFE exposure. The number of workers who were "ever exposed" to TFE was 4 773 and the number "never" exposed

amounted was 1 081. Standardised mortality ratios (SMR) were calculated for selected causes of death, including all causes and a number of cancers.

The calculated SMR estimates in this study had large confidence intervals and therefore there is some uncertainty regarding their reliability. In addition, all production sites also handled APFO and therefore it is not possible to exclude APFO as a cofounding factor. APFO has a harmonised classification as a category 2 carcinogen and a category 1B reproductive toxicant.

In comparison with national rates, the mortality rate from all causes (combined) and all cancers (combined) were lower than expected in the TFE exposed workers. SMRs were increased for liver (SMR = 1.27; 95 % CI 0.55-2.51), oesophageal (SMR = 1.23; 95 % CI 0.62-2.21), pancreatic (SMR = 1.15; 95 % CI 0.61-1.97) and kidney cancers (SMR = 1.44; 95 % CI 0.69-2.65), and for leukaemia (SMR = 1.48; 95 % CI 0.77-2.59) in the TFE exposed workers. A non-significant upward trend by cumulative TFE exposure was observed for liver cancer, but not for kidney cancer and leukaemia.

Animal studies

Two year carcinogenicity studies (similar to OECD TG 451) are available in which rats and mice were exposed via inhalation to TFE (NTP, 1997).

60 Fischer 344/N rats were exposed via whole-body inhalation to TFE (purity > 98 %) for 6 hours per day, 5 days per week for 104 weeks. 10 males and 10 females were assigned to the 15 month interim evaluation. The target chamber concentrations were at 0, 156, 312 and 625 ppm for males and 0, 312, 625, 1250 ppm for females. The measured chamber concentrations were found to be within 10 % of the range of the nominal concentration. For the kidney, a single section of each kidney was initially prepared for each animal. However, a further six to ten sections at 1 mm intervals were then prepared and assessed for each animal.

At the 15-month interim assessment, no effects on haematological, clinical chemistry or urinalysis parameters was observed. There was an increase in kidney weight in high dose animals. A statistically significant increase in incidences and severity of renal tubule degeneration was observed in males in all dose groups and in females in the mid and high dose groups. Renal tubule hyperplasia was also observed in 1/10 males in the mid and high dose groups and in 1/10 females in the mid dose group. An increase in liver weight was observed in females of the mid and high dose group. In the liver of all dose groups of males, there was also an increased incidence of clear cell foci and in the mid and high dose groups of females an increase of mixed cell foci was observed.

At study termination, the survival rates of the control, low, mid and high dose groups were 17/50, 12/50, 17/50 & 1/50 in males and 28/50, 16/50, 15/50 & 18/50 in females, respectively. There was a decrease in terminal body weight in high dose males and females (slight effect here). The terminal body weight as a percentage of the controls was 99 %, 99 % and 79 % for males and 97 %, 102 % and 91 % for females of the low, mid and high dose groups, respectively.

The only exposure related clinical finding was opacity of the eyes in females of the high dose group observed in 45/50 females (compared with 15/50 in the concurrent control), which was identified microscopically as cataracts.

In rats, a statistically and biologically significant increase in the incidence of multiple tumour types in the kidney and liver of both sexes was observed. In addition, an increase in mononuclear cell leukaemia was observed in female rats.

Detailed information on the incidences of neoplastic and non-neoplastic lesions seen in the kidney, liver and blood is given in Annex I of the CLH report.

Tumour incidences from the rat NTP study are summarised in Table 13 of the CLH report. Tumour incidences in historical control rats in 2-year NTP inhalation studies are reported in Table 14 of the CLH report.

***Table 1 of the CLH report**: Incidences of neoplastic lesions in rats following 2-year inhalation exposure to TFE (NTP, 1997).*

	Males				**Females**			
Dose group (ppm)	0	156	312	625	0	312	625	1 250
Number of animals examined	50	50	50	50	50	50	50	50
Kidney								
Single Sections:								
Renal tubule adenoma	0	0	6*	3	0	3	1	3
Renal tubule carcinoma	1	0	2	0	0	0	0	2
Renal tubule adenoma or carcinoma	1	0	6	3	0	3	1	5**
Step Sections:								
Renal tubule adenoma	2	4	3	11**	0	0	2	5*
Renal tubule carcinoma	0	1	0	0	0	0	0	1
Renal tubule adenoma or carcinoma	2	5	3	11**	0	0	2	5*
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*
Liver								
Hepatocellular adenoma	3	6	8	5	0	4*	5**	6**
Hepatocellular carcinoma	1	1	10**	3	0	4*	9**	2
Hepatocellular adenoma or carcinoma	4	7	15**	8	0	7**	12**	8**
Haemangiosarcoma	0	0	0	0	0	0	5*	1
Mononuclear Cell Leukaemia	34	43*	38	31	16	31**	23	36**
Testes: Interstitial cell adenoma	39	40	48**	47*	-	-	-	-
Mammary gland: Fibroadenoma	-	-	-	-	22	11*	9**	7**

* Significantly different from the control group (P ≤ 0.05); ** significantly different from the control group (P ≤ 0.01)

***Table 14 of the CLH report**: Incidences of neoplastic lesions in historical control rats in 2-year NTP inhalation studies as reported in NTP, 1997.*

	Males			**Females**		
Neoplastic lesion	Total	Mean ± SD	Range	Total	Mean ± SD	Range
Kidney						
Renal tubule adenoma	6/652	0.9 % ± 1.3 %	0 % - 4 %	1/650	0.2 ± 0.6 %	0 % - 2 %
Renal tubule carcinoma	0/652	-	-	1/650	0.2 ± 0.6 %	0 % - 2 %
Renal tubule adenoma or carcinoma	6/652	0.9 % ± 1.3 %	0 % - 4 %	2/650	0.3 % ± 0.8 %	0 % - 2 %
Liver						

	Males			Females		
Neoplastic lesion	Total	Mean ± SD	Range	Total	Mean ± SD	Range
Kidney						
Hepatocellular adenoma	20/653	3.1 % ± 2.8 %	0 % - 8 %	9/650	1.4 % ± 2.1 %	0 % - 6 %
Hepatocellular carcinoma	8/653	1.2 % ± 1.5 %	0 % - 4 %	1/650	0.2 % ± 0.6 %	0 % - 2 %
Hepatocellular adenoma or carcinoma	28/653	4.3 % ± 2.9 %	2 % - 9 %	10/650	1.5 % ± 2.0 %	0 % - 6 %
Mononuclear Cell Leukaemia	356/655	54.4 % ± 8.8 %	34 % - 66 %	262/653	40.1 % ± 7.2 %	30 % - 54 %
Haemangiosarcoma (all organs)	-	-	-	2/653	0.3 % ± 0.8 %	0 % - 2 %
Testes: Interstitial cell adenoma	450/655	68.7 % ± 8.7 %	54 % - 83 %	-	-	-

Groups of 58 B6C3F1 mice were exposed via whole body inhalation to TFE (purity > 98 %) for 6 hours per day, 5 days per week for 95-96 weeks. 10 males and 10 females were assigned to the 15 month interim evaluation. The target chamber concentrations were 0, 312, 625, 1 250 ppm (analytical concentrations were within a 10 % range).

At the 15 month interim assessment, no effect on haematological, clinical chemistry or urinalysis parameters was observed. A statistically significant increase in the incidence of renal tubule dilation was observed in males at the mid and high dose and in renal tubule karyomegaly in both sexes in the mid and high dose groups, which occurred in the absence of a change in kidney weight. In the liver, there was an increased incidence of angiectasis in all dosed groups, which was statistically significant in mid-dose males and low-dose females. There was a statistically significant increase in eosinophilic foci in mid and high dose females. There was an increased incidence of hepatic haemangiosarcomas in males in the high dose group (3/10) and in females of the low dose (1/10) when compared with the concurrent controls (0/10). There was also an increased incidence of hepatocellular adenoma and carcinomas in females of all dose groups in comparison to their absence in control females. A single case of histiocytic carcinoma has been observed in one high dose male.

At study termination, the survival rates of the control, low, mid and high dose groups were 38/48, 11/48, 2/48 and 1/48 for males and 36/48, 4/48, 6/48 and 4/48 for females. Due to the reduced survival the study was terminated during week 96.

A statistically and biologically significant increase in the incidence of histiocytic sarcoma and in the incidence of multiple tumour types in the liver was observed in both sexes. Both benign (e.g. renal tubule and hepatocellular adenomas and hepatic haemangiomas) and malignant (e.g. renal and hepatocellular carcinomas, hepatic haemangiosarcoma and histiocytic sarcoma) neoplasms were observed in both species and in both sexes.

Detailed information on the incidences of neoplastic and non-neoplastic lesions seen in the liver and of histiocytic sarcoma (at several organs) is given in Annex I of the CLH report.

Tumour incidences from the mouse NTP study are summarised in Table 15 of the CLH report. Tumour incidences in historical control mice in 2-year NTP inhalation studies are reported in Table 16 of the CLH report.

***Table 15 of the CLH report**: Incidences of neoplastic lesions in mice following 2-year inhalation exposure to TFE (NTP, 1997).*

	Males				Females			
Dose group (ppm)	0	312	625	1 250	0	312	625	1 250
Number of animals examined	48	48	48	48	48	48	47	47
Liver								
Hepatocellular adenoma	17	17	12	20	15	17	20*	15
Hepatocellular carcinoma	11	20**	33**	26**	4	28**	22**	20**
Hepatocellular carcinoma, multiple	4	9**	9**	6*	0	5**	7**	7**
Combined hepatocellular adenoma or carcinoma	26	34**	39**	35**	17	33**	29**	28**
Haemangioma	0	10**	5*	2	0	5*	2	1
Haemangioma, multiple	0	7**	2	1	0	1	1	0
Haemangiosarcoma	0	21**	27**	37**	0	27**	27**	34**
Haemangiosarcoma, multiple	0	16**	17**	18**	0	8**	12**	15**
Combined haemangioma or haemangiosarcoma	0	26**	30**	38**	0	31**	28**	35**
Haematopoietic system								
Histiocytic sarcoma (all organs)	0	12**	7**	7**	1	21**	19**	18**

* Significantly different from the control group (P ≤ 0.05); ** significantly different from the control group (P ≤ 0.01)

***Table 16 of the CLH report**: Incidences of neoplastic lesions in historical control mice in 2-year NTP inhalation studies as reported in NTP, 1997.*

	Males			Females		
Neoplastic lesion	Total	Mean ± SD	Range	Total	Mean ± SD	Range
Liver						
Hepatocellular adenoma	200/947	21.1 % ± 11.6 %	4 % - 46 %	114/937	12.2 % ± 9.7 %	0 % - 40 %
Hepatocellular carcinoma	184/947	19.4 % ± 5.8 %	9 % - 29 %	103/937	11 % ± 6.7 %	0 % - 30 %
Hepatocellular adenoma or carcinoma	358/947	37.8 % ± 12.5 %	11 % - 60 %	200/937	21.3 % ± 11.9 %	3 % - 54 %
Haemangioma	2/947	0.2 % ± 0.7 %	0 % - 2 %	1/937	0.1 % ± 0.5 %	0 % - 2 %
Haemangiosarcoma	12/947	1.3 % ± 1.7 %	0 % - 6 %	5/937	0.5 % ± 1.0 %	0 % - 3 %
Haematopoietic system						
Histiocytic sarcoma	6/950	0.6 % ± 1.2 %	0 % - 4 %	26/941	2.8 % ± 3.1 %	0 % - 10 %

The available inhalation repeated-dose toxicity and carcinogenicity studies with TFE identified the kidney, the liver and the haematopoietic system as target organs, confirming the distribution of TFE or its metabolites to these organs.

The available data in rats and mice demonstrate a statistically and biologically significant increase in the incidence of benign and malignant tumours in multiple organs in both sexes. A mechanism of tumour formation in kidney has been postulated and this mechanism is considered relevant to humans.

In vitro and *in vivo* studies indicate that TFE is metabolised by glutathione-S-transferases to *S*-(1,1,2,2-tetrafluoroethyl)glutathione (TFE-GSH) in the liver, which is released into the bile or recirculated to the kidneys where it is further metabolised to *S*-(1,1,2,2-tetrafluoroethyl)-*L*-cysteine (TFE-Cys). TFE-Cys is either activated by β-lyases to toxic species including difluoroacetic acid and difluorothio(no)acetic acid, which form covalent adducts with renal cellular proteins leading to nephrotoxicity. It may also be deactivated by *N*-acetyltransferases to form *N*-acetyl-*S*-(1,1,2,2-tetrafluoroethyl)-*L*-cysteine (TFE-NAc). TFE-NAc may be eliminated in the urine or undergo N-deacetylation, possibly reforming TFE-Cys which can subsequently be activated via β–lyases. In vitro and in vivo studies with TFE-Cys demonstrated similar nephrotoxicity to that observed with TFE and therefore it is postulated that this metabolic pathway is relevant for the renal toxicity observed in rodents. Isolated human proximal tubule cells were shown to be sensitive to TFE-Cys toxicity and therefore it cannot be excluded that this pathway is relevant for humans.

In vitro, glutathione conjugation of TFE was comparable between rats, mice and human hepatic fractions. Renal β-lyase activities were shown to be higher in rat than mouse or human kidney fractions whereas hepatic β-lyase activities were higher in mouse than rat or human liver fractions, which correlate with the target organs in rat and mouse studies. *N*-acetylase transferase activity was comparable in rat, mouse and human kidney fractions.

Workers at a production site which handled a number of organic fluorides including TFE had increased urinary levels of inorganic fluoride. Analysis of urine of rats and mice exposed to 6 000 ppm TFE for 6 hours found an increase in fluoride, cysteine conjugates (either TFE-Cys or TFE-NAc) and difluoroacetic acid. In both species excretion was complete within 48 hours. Similar urinary metabolites were observed when rats or mice were administered TFE-Cys.

The mechanism of tumour formation for the remaining tumour types observed in rats and mice has not been elucidated. However, based on the available data, the relevance for humans cannot be excluded.

The DS considered the tumour types observed as relevant for humans and the classification in category 1B warranted.

It is noted that TFE is a gas and the available animal carcinogenicity studies were conducted via whole body inhalation. The DS found that based on the available data it is not possible to conclusively prove that cancer is caused only by the inhalation route of exposure. For this reason, the hazard statement H350: May cause cancer, without specifying the route of exposure, is warranted.

Comments received during public consultation

In their comments Industry REACH Consortium (TFE Subgroup) expressed their agreement with the proposed classification and pointed to the self-classification as Carc. 1B. With regard to the requested harmonised classification proposal including the other hazards of the substance the DS in their response declared to limit the CLH proposal on carcinogenicity only. In their comment the cohort study was not judged as supporting the classification proposal. The consortium disagreed with the DS's proposal not to specify the inhalation route due to the physico-chemical properties of TFE.

One Member State commented on the interpretation of the tumour observed in the rat study which was reflected on by the DS. Another Member States agrees with the proposal on category 1B.

Assessment and comparison with the classification criteria

Comparison with the criteria

RAC agrees with the DS's observation that the available experimental carcinogenicity data demonstrate a causal relationship between TFE exposure in rats and mice and increased incidence of neoplasms. In rats, a statistically and biologically significant increase in the incidence of multiple tumour types in the kidney and liver of both sexes was observed. In addition, an increase in mononuclear cell leukaemia was observed in female rats. In mice, a statistically and biologically significant increase in the incidence of histiocytic sarcoma and in the incidence of multiple tumour types in the liver was observed in both sexes. Both benign (e.g. renal tubule and hepatocellular adenomas and hepatic haemangiomas) and malignant (e.g. renal and hepatocellular carcinomas, hepatic haemangiosarcoma and histiocytic sarcoma) neoplasms were observed in both species and in both sexes. The tumour types observed were considered relevant for humans. Therefore, classification as **carcinogen in category 1B** is warranted.

There is no evidence suggesting a genotoxic mode of carcinogenic action.

A mechanism of tumour formation in kidney has been postulated and this mechanism is considered relevant for humans. No mechanism of tumour formation has been identified for the other tumour types identified in rats and mice.

Therefore, it cannot be excluded that the increase in the incidence of mononuclear cell leukaemia and in neoplasms of the liver and haematopoietic system observed in rats and mice are relevant for humans.

RAC concurs with the factors in Table 18 (below) to be taken into consideration for this hazard assessment.

Table 18 of the CLH report*: Compilation of factors to be taken into consideration in the hazard assessment*

Species and strain	Tumour type and background incidence	Multi-site responses	Progression of lesions to malignancy	Reduced tumour latency	Response in single or both sexes	Confounding effect by excessive toxicity?	MoA and relevance to humans
Rat (Fischer F344/N).	↑ Renal tubule adenoma and carcinoma.	Yes Tumours observed in kidney, liver and blood.	Yes. ↑ Incidence of renal tubule hyperplasia (pre-neoplastic lesion). Renal tubule hyperplasia, adenoma carcinoma are a morphologic continuum.	-	Both sexes.	No The occurrence of regenerative epithelial changes associated with degenerative nephropathy were distinguishe	Non-genotoxic MoA assumed. TFE is metabolised in rat by glutathiones and β-lyases to nephrotoxic thiols. While the relevance of this pathway for
	↑ Mononuclear cell leukaemia.		Yes. Mononuclear cell leukaemia				

Species and strain	Tumour type and background incidence	Multi-site responses	Progression of lesions to malignancy	Reduced tumour latency	Response in single or both sexes	Confounding effect by excessive toxicity?	MoA and relevance to humans
			(malignant).			d from hyperplasia.	human toxicity has not been fully investigated, its relevance for humans cannot be excluded. For the remainder of the tumour types, the MoA has not been elucidated and therefore are assumed to be relevant for humans.
	↑ Hepatocellular adenoma and carcinoma.		Yes. ↑ Incidence of hepatocellular foci (pre-neoplastic lesion). Both adenoma (benign) and carcinoma (malignant) hepatic tumours observed.				
	↑ Hepatic haemangio sarcoma (mid dose females only). Not observed in NTP historical control females.		Yes. Hepatic haemangiosarcomas (malignant).		Female.		
	↑ Interstitial cell adenoma (mid and high dose males).		No		Male.		
B6C3F1 mice	↑ Hepatocellular adenoma and Carcinoma ↑ Hepatic haemangiomas. ↑ Hepatic haemangio sarcomas.	Yes. Tumours observed in liver and haematop-oietic system	Yes. ↑ Incidence of adenoma and haemangiomas (benign) and carcinoma and haemangiosarcoma (malignant) hepatic tumours observed.	Yes ↑ Hepatic haemangiosarcomas in high dose males at 15 months	Both sexes.	No	MoA has not been elucidated and therefore is assumed to be relevant for humans.
	↑ Histiocytic sarcoma (all organs).		Yes. Histiocytic sarcoma (malignant).	-			

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

RAC agrees with the DS that classification as carcinogen, category 1B is warranted as according to CLP Annex I, Section 3.6.2.2.3., the experimental data on animals are demonstrating "a causal relationship between the agent and an increased incidence of malignant neoplasms in (a) two or more species of animals".

Category 1A classification is not supported as the available cohort study due to its limitations does not allow to concluding on a causal relationship between TFE exposure and the development of tumours.

Category 2 should be considered appropriate if evidence of carcinogenicity in human studies or in animal studies is limited. The available information providing (clear) evidence of carcinogenicity in multiple organs of both sexes in two species does not support category 2.

RAC takes note of the proposal of the DS not to specify the route of exposure. TFE is a gas and the available information is only from whole body inhalation studies on rats and mice (where dermal or oral uptake may have contributed to the systemic availability to an unknown extent). No data on dermal/oral absorption rates are available and exposure via other routes cannot be excluded due to the lack of data.

Consonni *et al*. (2013) stated that the inhalation exposure is the only relevant route at the workplace (without having assessed a possible contribution via dermal exposure). IARC in their monograph (No 110) assessed the exposure of the general population as very low due to its flammability, thus direct dermal or oral exposure to the gaseous form may be considered as nonsignificant. TFE is not detectable in the polymerised products, but may be released (in particulate fumes) when e.g. coated pans are heated at very high temperatures. RAC agrees that the inhalation route should be considered as the most relevant route of exposure. Although TFE is a gas with high vapour pressure (32 395 hPa), other physicochemical properties such as slight water solubility (110 mg/L) and a $LogK_{ow}$ of 1.21 suggest that absorption via other routes of exposure cannot be excluded. Therefore, taking also into account the lack of data for the dermal/oral route, RAC in line with the DS's proposal and taking into account the CLP Annex I provisions (route of exposure is stated only where it is conclusively proven that no other routes of exposure cause the hazard) proposes that the classification should not be limited to the inhalation route.

RAC agrees with the DS that **classification as carcinogen, category 1B is warranted without any route specified.**

Specific concentration limit (SCL)

The DS did not consider SCL setting. However, RAC considers appropriate to discuss a SCL for TFE.

Based on Dybing *et al.* (1997), estimates of potency defined as the daily dose (in mg/kg bw) inducing a tumour incidence of 25% upon lifetime exposure (T_{25}) values were established and compared to the guidance level given in EC, 1999. The lowest dose at which significant tumour responses were observed was 312 ppm TFE in the carcinogenicity studies on rat and mouse (NTP, 1997). Tumours with high spontaneous incidences were regarded as of less relevance for the SCL calculation. The following table shows the calculated T_{25} values and the resulting potency class for the remaining tumour types in order to identify the lowest T_{25} value.

Table: SCL calculation

Species / sex	Tumour	Lowest dose with significant tumour response (ppm)	Net increase of incidence vs. control (%)	Dose corrected for 25% incidence (ppm)	Dose correction for 7 days of treatment (x(5/7))	Time correction (rat/none ; mouse x(96/104 wks)	Conversion ppm to mg/m³ (1 ppm TFE = 4.088 mg/m³)(25 C)	6 hour respiratory volume (m³/kg bw	Corresponding dose mg/kg bw for the SCL setting	Potency (EC, 1999)
Rat/ males	Liver/ combined adenoma and carcinoma	312	20	390	289	-	1139	0.29 (rat)	**330**	low
Rat/ females	Liver/ combined adenoma and carcinoma	312	14	557	398	-	1627	0.29 (rat)	472	low
Mouse/ males	Combined haemangioma or haemangio-sarcoma	312	26	300	214	198	809	0.5 (mouse)	404	low
Mouse/ females	Combined haemangioma or haemangio-sarcoma	312	31	252	180	166	678	0.5 (mouse)	339	low
Mouse/ males	Histiocytic sarcoma (all organs)	312	12	650	464	429	1.752	0.5 (mouse)	876	low
Mouse/ females	Histiocytic sarcoma (all organs)	312	20	390	279	257	1.051	0.5 (mouse)	526	low

The lowest T_{25} value (from combined adenoma and carcinoma of the liver of male rats) corresponds to 330 mg/kg bw. This T_{25} value is above 100 mg/kg bodyweight/day. This value could be indicative of a low potency of the substance. RAC takes the multiplicity of tumours and the short latency time (until first tumour occurrence) into account which contradicts a downgrading of the potency group. RAC concludes that the generic concentration limit (GCL) should be kept.

Additional references

Dybing, Sanner, Roelzema, Kroese, Tennant. T25: A Simplified Carcinogenic Potency Index: Description of the System and Study of Correlations between Carcinogenic Potency

and Species/Site Specificity and Mutagenicity Basic Clin. Pharmacol. Toxicol. 1997;80:272

EC. Commission working group on the classification and labelling of dangerous substances. Guidelines for setting specific concentration limits for carcinogens in Annex I of directive 67/548/EEC. Inclusion of potency considerations. Office for the Official Publications of the European Communities, Luxembourg, ISBN 92-828-7443-5, 1999

ECETOC. 2003. http://www.ecetoc.org/wp-content/uploads/2014/08/JACC-042.pdf (consulted on 08/08/2019).

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).