Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

Fluoroethylene

EC Number: 200-832-6
CAS Number: 75-02-5

CLH-O-0000007333-78-01/F

Adopted

8 June 2023

8 June 2023

CLH-O-0000007333-78-01/F

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: **fluoroethylene**

EC Number: **200-832-6**

CAS Number: **75-02-5**

The proposal was submitted by **France** and received by RAC on **26 August 2022.**

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

PROCESS FOR ADOPTION OF THE OPINION

France 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 **19 September 2022**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **18 November 2022**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Agnes Schulte, (supported by Advisers Frauke Hoffmann & Ulrike Gündel)**

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 **8 June 2023** 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	Fluoroethylene	200-832-6	75-02-5	Muta. 2 Carc. 1A	H341 H350	GHS08 Dgr	H341 H350			
RAC opinion	TBD	Fluoroethylene	200-832-6	75-02-5	Muta. 2 Carc. 1A	H341 H350	GHS08 Dgr	H341 H350			D
Resulting Annex VI entry if agreed by COM	TBD	Fluoroethylene	200-832-6	75-02-5	Muta. 2 Carc. 1A	H341 H350	GHS08 Dgr	H341 H350			D

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Fluoroethylene (vinyl fluoride; EC 200-832-6; CAS 75-02-5) is registered under the REACH Regulation and is manufactured in and/or imported to the European Economic Area, but details on tonnage levels are confidential. Information on the uses of the substance is not available. According to the IARC monograph, fluoroethylene has mainly been used in the production of polyvinylfluoride (PVF) and other fluoropolymers (IARC, 2008: https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono97.pdf).

The dossier submitter (DS) proposed harmonised classification of fluoroethylene as Muta. 2 and Carc. 1A.

Currently, the substance has no harmonised classification, but it is self-classified (summary) as Flam. Gas. 1, H220; Press. Gas (Liq), H280; Muta. 2, H341; Carc. 1B, H350; STOT RE 2, H373 (liver) according to the C&L inventory.

Physicochemical properties

In table 5 of the CLH dossier, the physicochemical properties of fluoroethylene are listed. Here, the vapour pressure of the substance is stated as 1.71 mPa at 25°C. A QSAR analysis using the EPI Suite model EPA MPBPWIN v1.43 is reported on the ECHA website as the source for this value. In table 17 of the CLH dossier, in which the physicochemical properties of 3 haloethylenes (vinyl halides) are compared, the vapour pressure of fluoroethylene is stated as 2.55 mPa and neither the temperature nor a reference for this value is given.

In the IARC monograph on the Evaluation of Carcinogenic Risks to Humans, No. 97 (IARC, 2008) "1,3-Butadiene, Ethylene Oxide and Vinyl Halides (Vinyl Fluoride, Vinyl Chloride and Vinyl Bromide)", a vapour pressure of 2.55 mPa at 21°C is reported for fluoroethylene. Accordingly, in the "PubChem" database[1], the vapour pressure of the substance is reported to be 2.4 mPa at 21°C as listed in Kirk-Othmer Encyclopedia of Chemical Technology (1994, 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V11: 684). In addition, a value of 2.55 mPa without giving a respective value for the temperature is reported on the "PubChem" website with reference to the website of the "The National Institute for Occupational Safety and Health (NIOSH)"[2] and the website of the "Occupational Safety and Health Administration (OSHA)"[3]. For any of these values the methodology for determination is reported.

Toxicokinetics

Absorption/distribution

Toxicokinetic studies according to an OECD test guideline (TG) are not available for fluoroethylene. Nevertheless, several studies obtained from the scientific literature are available which give indications that fluoroethylene is readily absorbed after inhalation (Filser & Bolt, 1979, 1981; IARC, 1995 and, 2008). Additional information on the low solubility in tissue and blood

[1] https://pubchem.ncbi.nlm.nih.gov/compound/6339#section=Vapor-Pressure
[2] https://www.cdc.gov/niosh/npg/npgd0660.html
[3] https://www.osha.gov/chemicaldata/567

suggests that the substance is rapidly equilibrated within the body after inhalation. Fluoroethylene is assumed not to accumulate in adipose tissue due to its rather low fat:blood coefficient of 2.4, which was determined *ex vivo* (Cantoreggi & Keller, 1997). Fluoroethylene further has a low volume of distribution, as the blood:air and tissue:air coefficients were determined to be low (0.54-1.82) (Cantorreggi & Keller, 1997).

Metabolism

Initially, fluoroethylene is oxidised to fluoroethylene oxide, probably mediated by cytochrome P450 (CYP) 2E1, as indicated by the inhibition of the metabolism of fluoroethylene using the CYP2E1-specific inhibitor 4-methylpyrazole (Cantoreggi & Keller, 1997). In rats, induction of CYP2E1 using ethanol, a known CYP2E1-inducer, increased the metabolic capacity by two to three-fold (Cantoreggi & Keller, 1997). Pharmacokinetic data indicate that in rats the metabolism of fluoroethylene is saturated at about 75 ppm (~140 mg/m³) in a closed system (determined by extrapolating the intersection of observed zero-order and first-order declines) (Filser & Bolt, 1979).

Cantoreggi and Keller (1997) demonstrated that microsomes of mice metabolised fluoroethylene more rapidly than microsomes of rats (V_{max} = 3.5 and 1.1 nmol/hr per mg protein, respectively) when exposed *in vitro* to fluoroethylene gas in closed chambers in the presence of a reduced nicotinamide adenine dinucleotide phosphate (NADPH)-regenerating system. Microsomes obtained from human livers were found to metabolise fluoroethylene at a similar rate compared to rats (range: 0.5–1.3 nmol/hr per mg protein), but one sample was similar to mice (3.3 nmol/hr per mg protein). V_{max} values were directly related to microsomal content of CYP2E1. Similarly to chloroethylene, fluoroethylene was shown to mediate the nicotinamide adenine dinucleotide phosphate (NADP)-dependent inactivation of CYP-450 *in vitro*.

Fluoroethylene oxide can re-arrange to fluoroacetaldehyde. Based upon the knowledge on similar substances, it is likely that fluoroacetaldehyde is metabolised to fluoroacetic acid, a potent inhibitor of the citric acid cycle. Incorporation of fluoroacetate into the citric acid cycle disrupts energy metabolism and leads to increased production of mitochondrial acetyl coenzyme A and, hence, excretion of ketone bodies, such as acetone. Accordingly, administration of fluoroethylene has been shown to increase acetone exhalation by rats (Filser *et al*, 1982).

It was shown that the toxicity of fluoroethylene is mediated via epoxide formation: Oxidative metabolism of inhaled fluoroethylene in the presence of Aroclor 1254, a hepatic cytochrome P-450 inducer, resulted in enhanced toxicity (Conolly *et al*, 1978, cited in Cantoreggi and Keller 1997). In addition, administration of trichloropropylene oxide, an inhibitor of the epoxide hydrolase, also increased fluoroethylene toxicity (Conolly and Jaeger 1977, cited in Cantoreggi and Keller 1997).

Fluoride appears to be a metabolite of fluoroethylene, as in several studies elevated fluoride excretion was detected in urine of rats and mice after exposure to fluoroethylene (Dilley *et al*, 1974; Bogdanffy *et al*, 1990 and 1995). Urinary excretion of fluoride was concentration-dependently increased in rats exposed to fluoroethylene via inhalation (Bogdanffy *et al*, 1990). The study authors reported a plateau in urinary fluoride excretion at approximately 2000 ppm. As hepatic cell proliferation in male and female rats and mice was also dependent on the test concentration with a plateau at concentrations of approximately 2000 ppm, the study authors suggested saturation of the fluoroethylene metabolism, i.e. of the hepatic cytochrome P450-mediated oxidation. Similarly, when rats and mice were exposed to 0, 25, 250 or 2500 ppm (corresponding to 0, 47, 470 or 4700 mg/m³) fluoroethylene for 18 months, a plateau of urinary excretion of fluoride was seen at ≥250 ppm (Bogdanffy *et al*, 1995).

Elimination

Elevated fluoride excretion was detected in urine of rats and mice in several studies (Dilley *et al*, 1974; Bogdanffy *et al*, 1990 and 1995). Fluoride concentrations in rat urine showed a statistically significant increase at 6 days after a 30-minute exposure to fluoroethylene (Dilley *et al*, 1974). An additional statistically non-significant increase in fluoride urine levels was observed on days 12 after exposure (Figure 1). The study authors suggested that either "fluoride ion or the fluorocarbons (or a metabolite, perhaps) are being stored in a compartment with a turnover rate of about 5 days". Moreover, it was shown that urinary excretion of fluoride is concentration-dependently increased in rats exposed to fluoroethylene for 45 and 90 days, respectively, via inhalation (0, 200, 2000 or 20000 ppm fluoroethylene, corresponds to 0, 376, 3760, or 37600 mg/m³ fluoroethylene; six hours/day, five days/week) (Bogdanffy *et al*, 1090). It was noted that urinary fluoride concentrations were consistently higher after 90 days of exposure to fluoroethylene compared to the 45-day exposure. As explained above, the data are also indicative of saturation of the fluoroethylene metabolism, i.e. of the hepatic cytochrome P450-mediated oxidation, and thus of saturation of the urinary excretion of fluoride in rats and mice (Bogdanffy *et al*, 1990 and 1995).

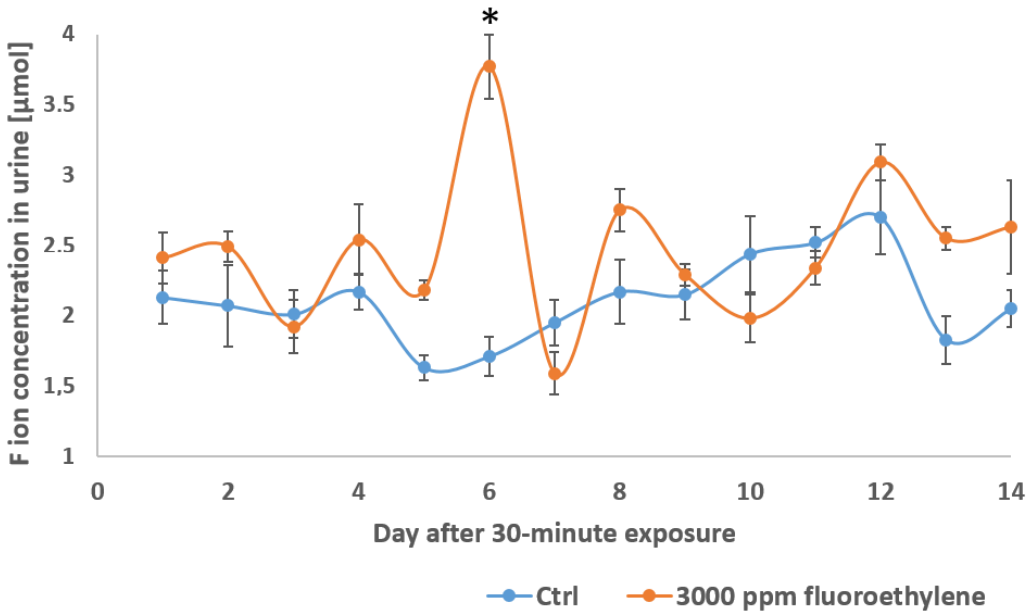

Figure 1: Daily fluoride ion excretion (µmol; mean ±SD) by male rats after 30 minutes of inhalation of fluoroethylene at 3000 ppm.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

Based on positive results in a reliable *in vivo* micronucleus assay, supported by positive results from *in vitro* mutagenicity assays, and, as the criteria for Muta. 1A/B are not considered to be fulfilled, the DS proposed classification of fluoroethylene as suspected of causing heritable mutations, i.e. Muta. 2 (H341), according to the CLP Regulation.

In vitro data

Fluoroethylene was considered by the DS to induce gene mutations *in vitro*. A mammalian cell gene mutation assay (Anonymous 1986b) according to OECD TG 476 performed with fluoroethylene was considered to be positive in the presence of metabolic activation using the S9 system. The DS further reported inconsistent findings in several Ames assays (Anonymous 1979a, Anonymous 1976, Anonymous 1979b) with the substance. All available Ames assays were considered not to be reliable.

Based on positive results obtained in an *in vitro* mammalian chromosome aberration test (Anonymous 1986a) according to OECD TG 473 and considered reliable, the DS concluded that fluoroethylene induces chromosome aberrations *in vitro* with metabolic activation.

In vivo data (mammalian somatic cells)

In an inhalation *in vivo* mammalian erythrocyte micronucleus test according to OECD TG 474 (Anonymous 1987) and considered reliable by DS, fluoroethylene induced micronuclei in bone marrow cells of female mice at the 24-hour sampling time.

In vivo data (mammalian germ cells)

In a rodent dominant lethal test performed similarly to OECD TG 478 (Anonymous 1988a) via the inhalation route in rats and considered reliable by DS, fluoroethylene did not increase the frequency of dominant-lethal mutations. The DS concluded that fluoroethylene was not mutagenic to germ cells in the male rat.

The DS further reported two *in vivo* indicator tests performed in germ cells, namely an unscheduled DNA synthesis (UDS) test in rat spermatocytes (Anonymous 1990) and an alkaline elution assay in testicular cells (Anonymous 1991) of exposed rats. Both tests yielded negative results.

In addition, a positive *Drosophila* sex-linked recessive lethal (SLRL) assay according to OECD TG 477 (Anonymous 1988b) is listed by the DS.

Based on the available data, the DS concluded that the classification criteria for Muta. 1B are not fulfilled for the following reasons: (i) The substance was negative in an *in vivo* germ cell mutagenicity study in mammals and (ii) studies related to DNA damage and/or repair were negative in testicular cells of rats. (iii) There are positive results in an *in vivo* micronucleus assay in female mice but there are no specific data regarding the ability of the substance or its metabolite(s) to interact with genetic material of germ cells. (iv) As the guideline for the *Drosophila* SLRL assay, which was positive for fluoroethylene, was deleted from the OECD test guideline programme, this study is not used for classification purposes.

Based on the positive result in female mice in an *in vivo* micronucleus assay and supported by positive findings in *in vitro* mutagenicity assays the DS concludes that classification as Muta. 2 of fluoroethylene according to CLP is justified.

The DS further noted that the fact that fluoroethylene presents higher mutagenic properties in systems with metabolic activation is consistent with the fact that the substance is expected to be metabolised into epoxides.

Comments received during consultation

One comment was received by a MSCA regarding germ cell mutagenicity supporting of a Muta. 2 classification based on the available data in the dossier.

Assessment and comparison with the classification criteria

In vitro data

There are three bacterial reverse mutation assays available performed with fluoroethylene (Anonymous, 1979a; Anonymous, 1976; Anonymous, 1979b). Mainly due to reporting deficiencies, all three assays are considered not assignable or not reliable. Overall, the three assays yielded inconsistent results. In the test by Anonymous 1979a fluoroethylene was considered mutagenic for strain TA1535 in the presence of an activation system.

The potential of fluoroethylene to induce gene mutations was confirmed with an *in vitro* mammalian cell gene mutation test using the Hypoxanthine Phosphoribosyltransferase (*Hprt*) gene (Anonymous 1986b) which was performed according to OECD TG 476 and GLP and is considered reliable. The test yielded concentration-dependent significant increases in mutant frequencies at all included test concentrations (20, 40, 60, 80 and 100%) compared to the concurrent negative control with metabolic activation in the absence of cytotoxicity. The test result is considered by RAC to be positive, consistent with the conclusion of the DS, and shows that fluoroethylene induces gene mutations *in vitro* in mammalian cells with metabolic activation.

Further, fluoroethylene was tested in an *in vitro* mammalian chromosome aberration test (Anonymous 1986a), similarly to OECD TG 473 under GLP conditions, leading to what are considered to be robust results with metabolic activation. However, the test regime is considered not to allow a thorough evaluation without metabolic activation as a continuous exposure was not performed. After a two-hour treatment with metabolic activation, significantly increased chromosome aberrations compared to the concurrent negative control at test concentrations ranging from 8.3 to 63% were detected. Severe cytotoxicity was evident at ≥ 61.3% if metabolic activation was used. Since an induction of chromosome aberrations was already observed at concentrations inducing moderate cytotoxicity, the test is regarded as positive albeit the treatment time of two-hours was shorter than specified in OECD TG 473 (3-6 hours). Thus, RAC concludes, in agreement with the DS, that fluoroethylene also induces chromosome aberrations *in vitro* in mammalian cells with metabolic activation.

In vivo data

Table 1*: In vivo mutagenicity/genotoxicity studies with fluoroethylene*

Study	Test substance and dose levels	Results	Reliability (RAC assessment)
Mammalian erythrocyte micronucleus test Anonymous 1987 (unpublished study report) OECD TG 474, GLP mouse (Crl:CD®-l(ICR)BR) male/female, 15-18/sex/dose, exposure 6h/day once, sampling 24, 48 and 72 h after end of exposure	**Fluoroethylene** Concentrations: 50100, 191000, 388000 ppm (inhalation, analytical concentrations)	**Positive** Concentration-dependent significant increase in frequency of micronucleated polychromatic erythrocytes compared to concurrent controls in females at 24-hour sampling time; equivocal in male mice Toxicity/Cytotoxicity: clinical signs and weight loss; no decrease in PCE/NCE ratio No data on historical positive and negative controls	**Test considered relevant and reliable; positive result considered robust** **Result regarded as positive, but not 'clearly positive' as historical control data not available** Further deficiencies: only 2000 instead of 4000 PCE scored

Study	Test substance and dose levels	Results	Reliability (RAC assessment)
Rodent dominant lethal test Anonymous 1988a (unpublished study report) OECD TG 478, GLP rat (CDF), male, 40/dose, exposure 6h/day for 5 consecutive days	**Fluoroethylene** Concentrations: 200, 2000 20000 ppm (inhalation)	**Negative** No increase in the frequency of dominant-lethal mutations Toxicity: no clinical signs	**Test considered relevant and reliable**
UDS test in spermatocytes Anonymous 1990 GLP rat (CDF), male, 15/dose, exposure 6h/day for 1, 2 or 5 consecutive days; sampling 2, 6 and 24 h after end of exposure	**Fluoroethylene** Concentrations: 20000 ppm (inhalation, nose only)	**Negative** Induced UDS not observed	**Test system not relevant for classification purpose** **No OECD guideline available (OECD TG 486 only validated for liver cells but not spermatocytes)** Further deficiencies: only one concentration level tested
Alkaline elution assay in testicular cells Anonymous 1991 GLP rat (Sprague Dawley), male, 4/dose, exposure 6h/day for 1, 2 or 5 consecutive days, sampling 2, 6, and 24 h after end of exposure	**Fluoroethylene** Concentrations: 20000 ppm (inhalation, nose only)	**Negative** No significant increase in single strand breaks or cross links in testicular DNA	**Test system not relevant for classification purpose** **No OECD guideline available (OECD TG 489 not validated for germ cells)** Further deficiencies: only one concentration level tested
Sex-linked recessive lethal (SLRL) test in *Drosophila melanogaster* Anonymous 1988b (unpublished study report) OECD TG 477, GLP *Drosophila melanogaster*, male, 200/dose, 24h exposure	**Fluoroethylene** Concentrations: 50% (inhalation)	**Positive** If exposed, 2.41% lethality produced compared to 0.08% in the concurrent negative control Toxicity/Cytotoxicity: none	**Test system not relevant for classification purpose** **OECD TG 477 was deleted by OECD in 2014** Further deficiencies: only one lower concentration level tested

Five *in vivo* genotoxicity tests reported by DS which were performed with fluoroethylene.

Two mutagenicity *in vivo* tests, one in somatic and one in germ cells, namely a mammalian erythrocyte micronucleus test (OECD TG 474, Anonymous 1987) and a rodent dominant lethal test (OECD TG 478, Anonymous 1988a), are considered to be relevant for classification purposes. Both tests were performed according to the respective OECD guidelines and GLP and are considered to be reliable.

The remaining three *in vivo* genotoxicity tests, namely an SLRL test in *Drosophila melanogaster* (OECD TG 477, Anonymous 1988b), an alkaline elution assay in testicular cells (Anonymous 1991) and a UDS test in spermatocytes (Anonymous 1990) are considered not relevant for classification purposes by RAC. The OECD TG 477 is not a test system in mammalian cells and was deleted in April 2014 following an OECD Council decision. There are currently no OECD TGs available for the alkaline elution assay in testicular cells and the UDS test in spermatocytes. In fact, it is stated in OECD TG 489 (paragraph 10) that "*Whilst there may be an interest in genotoxic effects in germ cells, it should be noted that the standard alkaline comet assay as described in this guideline is not considered appropriate to measure DNA strand breaks in mature germ cells*". The specificity of the applicability of OECD TG 486 is expressed in the title of the TG, as follows "Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells *In Vivo*".

The *in vivo* ***mammalian erythrocyte micronucleus*** test (Anonymous 1987) was performed in mice using the inhalation route (six hours/day) with the following three concentrations of fluoroethylene 50100, 191000 and 388000 ppm. Three sampling times (24, 48 and 72 h) after treatment were applied. The number of detected micronucleated polychromatic erythrocytes (MN-PCEs) in control and treated male and female mice are shown in Table 1. At the 24 h sampling time the frequency of MN-PCEs was significantly increased in females at the mid and high concentrations (191000 and 388000 ppm) compared to concurrent controls when 2000 PCEs were scored. Moreover, concentration-dependence was observed confirmed by a significant trend test. The test with male animals is interpreted as equivocal, however, only 2000 instead of recommended 4000 PCEs were scored for incidence of MN-PCEs. Overall, no significant depression of the ratio of PCEs to normochromatic erythrocytes (NCE) was found in the exposed mice. This indicates no confounding cytotoxicity. As historical positive and negative control data are not shown in the available data, it cannot be assessed if the test was clearly positive according to the guideline OECD TG 474 (section 47). Nevertheless, based on the clear concentration-relationship and the three-fold increase in the frequency of MN-PCEs in treated female mice the RAC considers the result as biological relevant and judges the test as positive. Thus, the RAC concludes that fluoroethylene was mutagenic in this *in vivo* somatic cell mutagenicity test.

Table 2*: NAMN-PCE values in in vivo mammalian erythrocyte micronucleus test with fluoroethylene in mice after 24 h, 48 h and 72 h sampling time*

Test substance	**24 h MN-PCEs/1000 PCEs (2000 PCEs scored)**	**48 h MN-PCEs/1000 PCEs (1000 PCEs scored)**	**72 h MN-PCEs/1000 PCEs (1000 PCEs scored)**
6 hours exposure, n=5 (or = 6 at 388000 ppm), **females**			
0	1.7 ± 1.1#	2.0 ± 0.7	2.8 ± 0.4
50100 ppm	3.0 ± 0.9#	1.4 ± 0.7	1.0 ± 0.5
191000 ppm	5.5 ± 1.2*#	2.8 ± 0.4	1.2 ± 0.4
388000 ppm	5.6 ± 0.6*#	1.8 ± 0.7	2.5 ± 0.8
CP (pos. control)	9.8 ± 1.2**		
6 hours exposure, n=5 (or = 6 at 388000 ppm), **males**			
0	2.8 ± 0.5	1.6 ± 0.9	2.0 ± 0.3
50100 ppm	4.5 ± 0.6	2.2 ± 0.9	1.8 ± 0.5
191000 ppm	3.3± 0.7	2.4 ± 1.0	1.2 ± 0.4
388000 ppm	4.7 ± 0.8	1.3 ± 0.3	0.8 ± 0.5
CP (pos. control)	8.4 ± 2.9**		
* p<0.05 ** p< 0.01 # trend significant			

The ***rodent dominant lethal test*** (Anonymous 1988a) was performed in rats using the inhalation route (six hours/day and for five consecutive days) with the concentrations of 200, 2000 and 20000 ppm fluoroethylene. The test substance did not increase the frequency of dominant-lethal mutations at all test concentrations and the test is interpreted by RAC to yield negative results. **RAC concludes that fluoroethylene is not mutagenic to germ cells in male rats.**

Comparison with the criteria

Classification criteria for mutagenicity, category 1A

No epidemiological studies are available for fluoroethylene. The DS did not propose read-across from structural analogues such as chloroethylene or bromoethylene. RAC notes that toxicity data on chloroethylene (and bromoethylene) indicate that both substances induce mutagenic effects in animals; however, none of the two substances have a harmonised classification for this hazard class. Because of the fact that, to date, the substances have not been assessed for this hazard class under CLP, it is unknown whether the mutagenicity data on these analogues could be sufficient for classification of the target substance, fluoroethylene, as Muta. 1A, H340. Thus, no classification in Cat. 1A in warranted.

Classification criteria for mutagenicity, category 1B

No positive heritable germ cell mutagenicity tests are available for fluoroethylene. Moreover, even if there were positive results from an *in vivo* somatic cell mutagenicity test in mammals, there is no further evidence that the substance has potential to cause mutations to germ cells, which would be prerequisite to justify a Cat. 1B classification (Table 3.5.1 of Annex I to the CLP Regulation). Thus, no classification in Cat. 1B is warranted.

Classification criteria for mutagenicity, category 2

There is positive evidence from a reliable *in vivo* somatic cell mutagenicity test in mammals with fluoroethylene, namely a positive *in vivo* mammalian erythrocyte micronucleus test in mice. Positive evidence from an *in vivo* somatic cell mutagenicity test in mammals is listed as a standalone criteria sufficient for classification in category 2 Table 3.5.1 of Annex I to the CLP Regulation). Moreover, the positive *in vivo* result in the micronucleus test is supported by positive *in vitro* findings showing that fluoroethylene induces chromosome aberrations also in mammalian cells. There is no negative *in vivo* genotoxicity/mutagenicity test available leading to inconsistent results in somatic mammalian cells. The available data are considered to be clear and conclusive. Thus, RAC, in agreement with the DS, concludes that **classification of fluoroethylene as suspected of causing heritable mutations, i.e. germ cell mutagen Category 2 (Muta. 2, H341) is warranted.**

RAC evaluation of carcinogenicity

Summary of the Dossier Submitter's proposal

To assess the carcinogenicity of fluoroethylene, two guideline (US-EPA Toxic Substance Control Act Guidelines, EPA OTS 798.3300) and GLP compliant carcinogenicity studies in rats and mice with inhalation exposure to fluoroethylene gas (purity > 99.4%; whole-body; test concentrations: 0, 25, 250 and 2500 ppm) are available.

In these studies, benign and malignant tumours in different tissues of rats and mice were observed after inhalation exposure to fluoroethylene.

In rats and mice of both sexes, exposure caused statistically significant increases in the incidence of cancer of the blood vessels and of the liver (hepatic haemangiosarcomas) at concentrations ≥250 ppm fluoroethylene.

In rats, fluoroethylene inhalation additionally resulted in increased incidences of benign liver tumours (hepatocellular adenomas) and cancer of the Zymbal gland (carcinomas) in both sexes (statistically significant in female rats after 18 months of exposure to 2500 ppm fluoroethylene). Metastases were frequently found in the lungs. Increased incidence of malignant liver tumours (hepatocellular carcinomas) in female rats at the high dose (2500 ppm) was observed as well, but differences were not statistically significant, although this tumour type was not observed in control females.

Besides eliciting hepatic haemangiosarcomas, fluoroethylene inhalation resulted in additional dose-dependent increases in the incidence of bronchioalveolar adenomas in mice of both sexes (statistically significant at ≥250 ppm in males and at 2500 ppm in females). Statistically non-significant increases in incidence of hepatocellular adenomas at and above the lowest test concentration of 25 ppm in males and at 250 ppm in females were observed as well. In addition, exposure of mice to fluoroethylene also caused increases in incidence of mammary-gland cancer (primarily adenocarcinomas) in female mice without showing a dose-dependency. Increases in benign Harderian gland tumours (adenomas) in mice of both sexes were dose-dependent. Small focal areas of hypertrophy or hyperplasia of the Harderian glands were present in all male treatment groups and in 250 and 2500 ppm females.

Regarding tumour latency, the DS noted that in mice bronchioloalveolar adenomas had a relatively short latency to tumour onset and thus appeared to be the most sensitive indicator of the test substance-induced cancer. Extrahepatic haemangiosarcoma and haemangiomas in the peritoneum, mammary gland, ovaries, and epididymides (at 25 ppm only, without dose-response relationship) occurred only with reduced (lower) frequency and increased latency relative to the tumours in the liver (Table 7 and Table 8).

The DS highlighted that fluoroethylene is likely metabolised in a similar manner compared to chloroethylene and bromoethylene, which are both known carcinogens (harmonised classification for Carc. 1A and Carc. 1B, respectively), by oxidation via CYP450 followed by rearrangement to the acetaldehyde, which is oxidised to fluoroacetic acid. Fluoroethylene toxicity, as the toxicity of chloroethylene and bromoethylene, is mediated via epoxide formation, and epoxides can form covalent DNA adducts. Inhalation exposure of rats and mice to fluoroethylene produced a dose-related increase in the formation of the promutagenic adduct N2,3-ethenoguanine in their liver DNA (Swenberg et al, 1999). There is no data available suggesting that mechanisms by which fluoroethylene induces tumours in experimental animals is not relevant for humans. On the contrary, data suggests that human, rat, and mouse liver microsomes metabolise fluoroethylene similarly and at similar rates (Cantoreggi and Keller, 1997).

Regarding the possibility of a confounding effect of excessive toxicity at the concentrations tested, the DS noted that survival was decreased in male and female rats and mice. The DS, however, concluded that the high mortality that was particularly observed in the treatment groups and thus may be linked to carcinogenic effects rather than to an excessive toxicity at the tested concentrations. Besides the high mortality, other than sporadic differences of statistical significance only, there were no changes in mean body weight of exposed mice compared to controls during the first 372 days of the test. Mean body weight gain of 2500 ppm male mice was significantly decreased (-17%) relative to controls over the 1-372 day interval. Mean body weight gain of mice in the remaining exposure groups was similar to controls, indicating that mortality was probably not due to excessive toxicity at the tested concentrations.

The DS noted that fluoroethylene is mutagenic in Salmonella typhimurium TA1535 with the addition of a rat liver homogenate metabolic activation system. In addition, fluoroethylene induces gene mutations and chromosomal aberrations in Chinese hamster ovary cells (with metabolic activation). In vivo, sex-linked recessive lethal mutations in Drosophila melanogaster, and micronuclei in bone marrow cells of female mice were reported (IARC 1995).

Overall, the DS concluded that there is sufficient evidence from animal data regarding a carcinogenic potential of fluoroethylene, as exposure to fluoroethylene caused both benign and malignant tumours in several different tissues in two different species: rats and mice, in two reliable studies. In addition, there is evidence that fluoroethylene is mutagenic in somatic cells (see paragraph on genotoxicity). Thus, the DS considered the criteria for Carc. 1B as fulfilled. Accordingly, the NTP classified fluoroethylene as a reasonably anticipated human carcinogen based on sufficient evidence from carcinogenicity studies in experimental animals (NTP, 2000). The IARC concluded in their evaluation that fluoroethylene is probably carcinogenic to humans (Group 2A) based on sufficient evidence in animals and lack of evidence in humans (IARC, 2008).

In addition to the available data on fluoroethylene, the DS proposed read-across from the source substances bromoethylene and mainly chloroethylene. The DS concluded that even if there is no epidemiological data available for the target substance itself, fluoroethylene is expected to have the same carcinogenic properties as chloroethylene based on a weight of evidence approach taking into account structural similarity, toxicokinetics and toxicological considerations. In this context, the DS considered the absence of human data not as a lack of evidence of carcinogenic effects in humans, but rather concluded that classification of fluoroethylene as a Carc. 1A, H350, is justified based on read-across to chloroethylene.

Read-*Across *as proposed by the DS for the hazard class carcinogenicity

According to the CLP Guidance on the Application of the CLP Criteria (ECHA, 2017), "*in the absence of carcinogenicity data, read-across can be used to support a classification for carcinogenicity when the chemical in question is similar to a known or suspected carcinogen (Category 1A, 1B or 2). The similarity between chemicals is considered in terms of structural features, physico-chemical properties and overall toxicological profile……. (...)*

Any predictions made on the basis of read-across should take into account the totality of data on the chemicals in question, including the physico-chemical properties, toxicological profile, toxicokinetics, structural analogy and the performance of any (Q)SAR models used, in a weight of evidence approach driven by expert judgement. The final decision must be clear, scientifically defensible and transparent".

To assess the relevance of reading across from other haloethylenes (Figure 2) to fluoroethylene, the DS considered the following elements: 1) Chemical structure, physico-chemical properties and 2) toxicological profile.

1) Chemical structure and physico-chemical properties

Available evidence suggests that fluoroethylene is metabolised via the same pathway as that of the known carcinogens chloroethylene (vinyl chloride; CAS: 75-01-4) and bromoethylene (vinyl bromide; CAS: 593-60-2), to which it share also a similar chemical structure (NTP, 2000) (Figure 2) and comparable physico-chemical properties (Table 3).

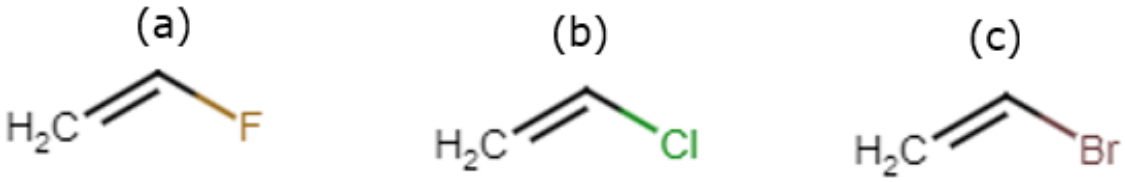

Figure 2: Chemical structures of (a) fluoroethylene (vinyl fluoride), (b) chloroethylene (vinyl chloride; harmonised classification for Carc. 1A, H350) and (c) bromoethylene (vinyl bromide, harmonised classification for Carc. 1B, H350).

***Table 3**: Physicochemical properties of the three haloethylenes.*

	Fluoroethylene (Vinyl fluoride)	**Chloroethylene (Vinyl chloride)**	**Bromoethylene (Vinyl bromide)**
Melting Point [°C] at 1013 hPa	-160.5 °C	-153.7°C	-137.8°C
Boiling Point [°C]	-72°C	-13.3°C	+15.8°C
Density [g/cm³]	0.636 g/cm³ at 25°C	0.911 g/cm³ at 20°C	1.493 g/cm³ at 20°C
Vapour pressure [Megapascal, MPa]	2.55 MPa (no temperature given) 19152 mmHg (no temperature given)	0.34 MPa (no temperature given) 2580 mmHg at 25°C	0.21 MPa at 37.8°C 1.033 mmHg at 25°C
Partition coefficient (log PoW)	0.8975 at 25°C	1.46 (no temperature given)	1.57 (no temperature given)
Water solubility [g/L] at 20°C	Slightly soluble 9.4 g/L at 80°C and 3.4 mPa	2.7 g/L	Insoluble

All three structurally similar substances belong to the class of simple haloethylenes and differ only by the halogen substituent (F, Cl or Br). Each halogen produces a similar donor mesomeric effect on the double bond and renders the substance reactive. Under anhydrous conditions, these compounds react easily with metals (Cu, Li, Mg) by insertion of metal between the halogen and the carbon. Overall, the DS proposed that, based on their physicochemical properties, they may elicit similar biological effects.

2) Toxicological profile

Metabolism

The metabolism of the three haloethylenes was shown to be similar:

The first step in the metabolism pathways for chloroethylene, bromoethylene and fluoroethylene is oxidation, which is predominantly mediated by human cytochrome CYP2E1. In this step, the highly reactive ethylene oxide compound is formed, which can spontaneously rearrange to the acetaldehyde derivate (Barbin *et al*, 1975; Holt *et al*, 2000; Cantoreggi & Keller, 1997; IARC, 2008). Pharmacokinetic data imply that the rate of biotransformation of fluoroethylene is about one-fifth that of chloroethylene (Bolt *et al*, 1981). Fluoroethylene is metabolised faster than bromoethylene, but slower than chloroethylene (Bolt *et al*, 1982). Chloroethylene and bromoethylene are metabolised to haloacetaldehydes. Similarly, besides fluoroethylene oxide, also fluoroacetaldehyde is a metabolite of fluoroethylene (IARC, 2008). Based upon the knowledge on chloroethylene metabolism, it is likely that fluoroacetaldehyde is metabolised to fluoroacetic acid, a potent inhibitor of the citric acid cycle. Incorporation of fluoroacetate into the

citric acid cycle disrupts energy metabolism and leads to increased production of mitochondrial acetyl coenzyme A and, hence, excretion of ketone bodies, such as acetone. Accordingly, administration of fluoroethylene has been shown to increase acetone exhalation by rats (Filser et al, 1982).

The metabolism of fluoeroethylene and chloroethylene appears to be saturable, their metabolites were shown to be able to bind to proteins, DNA and RNA and form etheno-adducts (ethylene oxide compound most reactive with nucleotides).

Fluoroethylene, similarly to chloroethylene, was shown to mediate NADP-dependent inactivation of CYP in vitro (Ortiz de Montellano et al, 1982).

Toxicity of fluoroethylene, chloroethylene and bromoethylene is mediated via epoxide formation.

Mutagenicity

Exposure of mice and rats to fluoroethylene results in the formation of N2,3-ϵG, one of the promutagenic adducts that may be implicated in the mutagenicity and carcinogenicity of the substance (IARC, 2008). In addition, there is positive evidence that fluoroethylene may be mutagenic in vitro (positive in bacteria and Chinese hamster ovary cells, particularly after metabolic activation). Positive results were also obtained in vivo (micronucleus assay in mice and SLRL assay in Drosophila melanogaster). In contrast, the available dominant lethal test in rats was negative. An overall assessment of in vitro and in vivo genotoxicity studies can be found in the section on mutagenicity.

Chloroethylene and bromoethylene are not classified for their mutagenicity properties. However, their harmonised classification predates CLP. Information reviewed by the IARC in 2008 points to similar mutagenic effects elicited by chloroethylene and bromoethylene compared to those reported for fluoroethylene.

The genotoxicity of chloroethylene has been clearly demonstrated in several in vitro and in vivo systems (in an Ames test, an in vitro recessive lethal test in Drosophila melanogaster, an in vivo micronucleus test in mice and two in vivo cytogenicity assays in hamsters). The in vivo chromosome aberration assay in rats, as well as the dominant lethal test in mice, as on the other hand, were negative. It has been suggested that negative results in the latter test could be attributed to the inability of chloroethylene or its active metabolites to reach germ cells in sufficient amounts to induce mutations. Chromosomal aberrations have also been observed in peripheral lymphocytes of exposed workers in some studies.

Bromoethylene has been shown to be mutagenic in bacteria and in vitro in Drosophila melanogaster germ cells. The comet assay with bromoethylene in the stomach, liver, kidney, bladder, lung, brain and bone marrow of male CD-1 mice yielded statistically significant increases in DNA damage in all organs except the bone marrow (IARC, 2008).

Overall, all three substances were shown to be mutagenic in somatic cells *in vitro* and/or *in vivo*. *In* vitro, mutagenic responses were generally more pronounced after metabolic activation, suggesting that metabolites are responsible of the mutagenic effects.

Carcinogenicity

The DK QSAR toolbox and the OECD QSAR Toolbox v.4.2 profilers both triggered alerts for the three haloethylenes, as mentioned by the DS. x

Epidemiological data

Epidemiological data is only available for chloroethylene. The DS reported the information as stated in the IARC monograph No. 97 (IARC, 2008) (for details see the CLH dossier) and, in line

with the IARC conclusion, concluded that "there is sufficient evidence in humans for the carcinogenicity of vinyl chloride [chloroethylene]. Vinyl chloride causes angiosarcomas of the liver and hepatocellular carcinomas."

Animal data

One chronic inhalation toxicity study with bromoethylene was presented in the CLH dossier. In this study, inhalation exposure of rats to bromoethylene caused a significant increase in the incidence of angiosarcomas of the liver, hepatocellular adenomas and carcinomas, and squamous-cell carcinomas of the Zymbal gland in both sexes. Epidemiological data for bromoethylene were not presented in the CLH dossier and, according to the IARC monograph (IARC, 2008), are not available for the substance.

The carcinogenicity of chloroethylene has been studied intensively in various species (rats, mice and hamsters) using numerous routes of administration (for details see Table 11). The studies used for read across are described in more detail in the carcinogenicity paragraph below. The studies with fluoroethylene in rats and mice (Bogdanffy et al, 1995) were assigned a Klimisch score of 1 by the DS.

Various tumours in the liver such as haemangiosarcoma / angiosarcoma, hepatocellular adenoma and carcinoma and carcinomas of the Zymbal gland were consistently found with all the three substances. Increased incidences of mammary gland tumours and lung tumours in mice were reported with fluoroethylene and with chloroethylene.

Some tumour types, however, only occurred after exposure to chloroethylene. Nevertheless, most of these tumours were observed in studies with hamsters. Studies in hamsters are only available for chloroethylene, but not for the other haloethylenes (bromoethylene and fluoroethylene), hampering a direct comparison.

Overall, the DS concluded the following regarding the available carcinogenicity data:

Epidemiological studies with occupational exposure to chloroethylene have shown that chloroethylene causes cancer of the liver blood vessels (hepatic angiosarcoma) in humans (IARC, 2008). In experimental animals, this type of cancer is usually referred to "liver angiosarcomas" or "hepatic haemangiosarcomas". All three considered haloethylenes (chloroethylene, bromoethylene and fluoroethylene) were shown to cause this type of tumours in mice and rats. The spectrum of lesions is thus similar among fluoroethylene, chloroethylene and bromoethylene. Moreover, all three halides, chloroethylene, bromoethylene and fluoroethylene, caused hepatocellular carcinomas or adenomas and Zymbal gland carcinomas in rats.

Chloroethylene and fluoroethylene were demonstrated to cause mammary gland and lung tumours in mice.

The IARC concluded that all available studies showed a consistent and similar response of fluoroethylene and chloroethylene and supported that fluoroethylene should be considered as a known human carcinogen, similarly to chloroethylene. DS concurred with this conclusion and proposed that fluoroethylene as chloroethylene should be considered as Carc. 1A, (H350) with regards to classification under CLP.

Mode of action

The metabolism of fluoroethylene, chloroethylene and bromoethylene are assumed to be similar. The substances are activated by CYP2E1 to (fluoro-, chloro-, bromo-)ethylene oxides, which rearrange to (fluoro-, chloro-, bromo-)acetaldehyde. These metabolites can react with nucleic acid bases and form adducts that may be implicated in mutagenicity and carcinogenicity.

The spectrum of neoplasms produced by the three haloethylenes in mice and rats of both sexes is strikingly similar (Mertens *et al*, 2017). The target organ common to these three substances is the liver. Chloroethylene caused angiosarcomas in the liver and hepatocellular carcinomas. Bromoethylene caused significant increases in the incidence of angiosarcomas of the liver, hepatocellular adenomas as well as carcinomas, and squamous-cell carcinomas of the Zymbal gland. Fluoroethylene caused haemangiosarcomas in the liver, hepatocellular adenomas and carcinomas and Zymbal gland carcinomas (IARC, 2008).

In summary, the DS concluded that all three substances, chloroethylene, bromoethylene and fluoroethylene, undergo a similar metabolism with the formation of reactive metabolites leading to similar promutagenic adducts, which in turn lead to carcinogenicity. The evidence of mutagenicity for these compounds was also noted in the genotoxicity studies, in which fluoroethylene, chloroethylene and bromoethylene exhibited mutagenic properties *in vitro* and/or *in vivo*. *In vitro*, a higher mutagenic response was obtained in the presence of an exogenous metabolic activation system, suggesting that metabolites are responsible of the mutagenic effects.

DS's conclusion on the applied read-across

Epidemiological studies regarding the carcinogenicity of fluoroethylene are not available. However, the substance was shown to act similarly to the known carcinogen chloroethylene, which induces liver angiosarcomas and hepatocellular carcinomas in animals and humans (IARC, 2008).

Fluoroethylene, chloroethylene and bromoethylene are metabolised to similar DNA-reactive intermediates (haloethylene oxide and haloacetaldehyde) via a cytochrome P450 2E1–dependent pathway and cause genetic damages in vivo and in vitro, as confirmed by the available genotoxicity dataset, in which positive results were reported in somatic cells for all three substances. Furthermore, the DNA adducts formed during metabolism of the three halides are similar, and the formed etheno adducts were shown to be able to cause DNA miscoding by modifying base-pairing sites (IARC 2008). The fact that bromoethylene, chloroethylene and fluoroethylene can all cause liver haemangiosarcoma in experimental animals and induce the formation of similar DNA adducts support a common mechanism for all three substances for induction of carcinogenic effects.

Overall, the DS concluded that fluoroethylene should be considered to act similarly to the known human carcinogen chloroethylene, which is classified as Carc. 1A (H350) according to CLP. Therefore, even in the absence of epidemiological data for fluoroethylene itself, the DS considers the level of evidence as sufficiently robust to classify fluoroethylene as Carc. 1A (H350) as well, based on a read-across from chloroethylene.

The DS did not report any uncertainties regarding the proposed read-across.

Comments received during consultation

One MS commented on this endpoint and supported the proposed classification for Carc. 1A (H350) based on read across to chloroethylene. The MS considered the criteria for the classification of fluoroethylene as Carc. 1B to be fulfilled, as sufficient evidence of carcinogenicity in experimental animals is demonstrated. The MS also considered the criteria for Carc. 1A as fulfilled for fluoroethylene based on a read-across from the structurally similar monohaloalkene chloroethylene (EC 200-831-0), which bears a harmonised classification of Carc. 1A (H350), based on the following reasons: (i) structural similarity, (ii) increased incidence of hepatic haemangiosarcoma in experimental animals treated with fluoroethylene or chloroethylene, consistent with epidemiological data in chloroethylene exposed workers and (iii) positive findings in genotoxicity tests in somatic cells and indications of similar genotoxic mode of action (CYP2E1-

dependent metabolic activation to yield reactive metabolites, which subsequently can form of etheno-DNA adducts). No SCL was proposed due to the applied read-across. The MS further mentioned that for the entry in Annex VI, the assignment of 'Note D' should be considered, as the harmonised classification of chloroethylene as Carc 1A (H350) in Annex VI, Part 3, Table 3 (Index No 602-023-00-7) also contains the 'Note D' (for details, please see the Background Document).

As the 'Note D' has been assigned to chloroethylene, it must be assumed that this substance is capable of spontaneous polymerisation or decomposition. Due to the structural similarity, it can be assumed that fluoroethylene might also be capable of spontaneous polymerisation or decomposition.
The database "ChemInfo (www.gsbl.de)" indicates that fluoroethylene is usually transported in a stabilised state. A possible transport of unstabilised fluoroethylene cannot therefore be excluded.
For this reason, the MS noted that 'Note D' should be considered for fluoroethylene as well.

Assessment and comparison with the classification criteria

RAC assessment of the available data on fluoroethylene

The carcinogenic potential of fluoroethylene has been studied in two combined repeated dose toxicity/carcinogenicity studies in rats and mice, respectively (see also Table 9 in the CLH report). The combined chronic toxicity/carcinogenicity studies in rats and mice (according to US-EPA EPA OTS 798.3300; GLP compliant; Klimisch 1 assigned by the DS) demonstrate that fluoroethylene causes liver tumours (among others haemangiosarcomas) in both species and in both sexes at all tested exposure concentrations, reaching statistical significance at ≥250 ppm (see Table 4 to Table 9).

RAC assessment of the available animal studies with fluoroethylene

Rat study (Anonymous,1992; Bogdanffy *et al*,1995)
Groups of 95 male and 95 female Crl:CD®BR rats were exposed to 0, 25, 250, or 2500 ppm of fluoroethylene gas via inhalation for 6 hours per day, 5 days per week, for up to 2 years, weekends and holidays excluded.

Benign and malignant tumours in different tissues of rats and mice were observed at the two interim sacrifices after 12 and 18 months of exposure, respectively, and at the final sacrifice at 24 months.

Slight to moderate decreases in mean body weight gain (6-15%) were noted among rats of the 25 and 250 ppm groups, but not in the 2500 ppm group, when the surviving rats were evaluated at final sacrifice (no individual data reported). RAC notes, however, that mortality – particularly during the second year of the study – was very high and survival of rats up to the final sacrifice was limited (≤ 20% survival in treatment groups, ~25% survival in controls), leading to an early sacrifice of the animals of the two highest dose groups before the planned termination of the study. This high mortality might have impacted the results on body weight obtained at study termination.

The DS considered the early mortality occurring in the second year of exposure being rather the result of haemorrhage from hepatic haemangiosarcoma than a confounding effect of excessive toxicity at the concentrations tested.

In rats, statistically significant early mortality was observed at ≥ 250 ppm in males and at all test concentrations in females (≤ 20% survival in treatment groups). The study authors stated that the high early mortality even precluded meaningful statistical evaluation of clinical

observations data among males of the 250 and 2500 ppm groups. In exposed animals, death was sudden and without clinical observation associated with morbidity. With the exception of 2 deaths related to haemangiosarcomas, no exposure-related increases in mortality occurred until after the 12-month interim sacrifice. Mortality related to test substance-induced hepatic haemangiosarcomas became more significant during the second year of exposure. The total incidences of male rats of the 0, 25, 250, and 2500 ppm groups that died due to haemangiosarcomas (hepatic and extrahepatic) over the course of the study were 1/80, 2/80, 25/80, and 15/80, respectively. These incidences in female rats were 0/80, 7/80, 14/80, and 15/80 at 0, 25, 250, and 2500 ppm, respectively. The DS concluded that the high mortality that was particularly observed in the treatment groups and, thus, may be linked to carcinogenic effects rather than to an excessive toxicity at the tested concentrations.

RAC notes that in the control groups mortality was also high in the second study year (around 75% at study termination). This clearly indicates that excessive toxicity due to exceedance of the MTD might not have been the reason for the high mortality, but rather points towards a general excess mortality in all study animals. Historical control data were not provided in the full study report available to the DS, hampering a detailed assessment of the excess mortality observed.

In OECD TG 453 it is stated that "termination of the study should be considered when the number of survivors in the lower dose groups or the control group falls below 25 per cent", indicating that the study at hand may still be used for hazard assessment, but may be of restricted reliability as the minimal criterion of 25% survival in the control group was almost reached and even undershot in the low-dose group. The US EPA OTS 798.3300 guideline on the other hand states that: "the number of animals at the termination of the study should be adequate for a meaningful and valid statistical evaluation of long-term exposure". This criterion was not met, as indicated by the study authors. Moreover, EPA OTS 798.3300 states that "for a valid interpretation of negative results, it is essential that survival in all groups does not fall below 50 percent at the time of termination" (i.e. 18 months for mice and 24 months for rats). As the present study in rats yielded positive results, the generally high mortality may thus not be that important, when considering the obvious increases in tumour incidences in treated animals only.

RAC notes, however, that the generally high mortality in this study increases the uncertainties regarding the reliability of the study results. Nevertheless, RAC considers the reported increases in tumour incidences as clearly substance related for the reasons explained above.

There were no biologically significant effects on haematological, clinical chemical, or urinalysis parameters measured in rats at any of the evaluations.

Urinary fluoride excretion was concentration- and time-dependently increased.

At necropsy, the following main gross observations were made in rats that were related to substance exposure: masses, nodules, discoloration and haemorrhage of the liver; mass/nodules and discoloration of the lungs, fluid of the peritoneal cavity; masses of the head, face and perioral area; abscesses of the face.

Non-neoplastic lesions, with increased incidences in treated animals, were foci of hepatocellular alteration (in all male treatments and at 250 and 2500 ppm in female rats) and sinusoidal dilatation (observed in all treatment groups). Microscopically, these lesions were correlated with the observed tumours in treated rats: hepatic haemangiosarcoma, hepatocellular adenoma and carcinoma, metastatic lung tumours, and Zymbal's gland tumours (tumour originating from an auditory sebaceous gland that opens into each external ear canal known as Zymbal's gland). The incidences of these lesions were mostly concentration-dependent and seen in all treatment groups (Table 4 and Table 5).

***Table 4**: Neoplastic microscopic observations in target organs of male and female rats necropsied during a) 0-12 months, b) 13-18 months and c) 19-24 months[a].*

a)

0-12 months	Concentrations			
Dose (ppm):	0	25	250	2500
Male rats				
Liver				
Carcinoma, hepatocellular	0/18	0/15	0/14	1/17
Zymbal's gland				
Carcinoma, sebaceous/squamous cell	**0/18**	**0/5**	**0/5**	**4*/17**
Female rats				
Liver				
Haemangiosarcoma	0/12	0/14	0/14	2/18
Zymbal's gland				
Carcinoma, sebaceous/squamous cell	0/12	0/5	0/5	4/18

b)

13-18 months	Concentrations			
Dose (ppm):	0	25	250	2500
Male rats				
Liver				
Haemangiosarcoma	**0/18**	**1/21**	**11*/25**	**12*/40**
Adenoma, hepatocellular	1/18	1/21	2/25	3/40
Carcinoma, hepatocellular	1/18	0/21	1/25	1/40
Zymbal's gland				
Carcinoma, sebaceous/squamous cell	0/18	2/13	1/15	5/40
Female rats				
Liver				
Haemangiosarcoma	**0/24**	**2/26**	**10*/33**	**12*/44**
Adenoma, hepatocellular	0/24	1/26	5/33	0/44
Carcinoma, hepatocellular	0/24	0/26	0/33	3/44
Zymbal's gland				
Carcinoma, sebaceous/squamous cell	**0/24**	**0/16**	**1/24**	**6*/44**

c)

19-24 months	Concentrations			
Dose (ppm):	0	25	250	2500
Male rats				
Liver				
Haemangiosarcoma	0/44	4/44	19/41	8/23
Adenoma, hepatocellular	0/44	3/44	2/41	1/23
Carcinoma, hepatocellular	3/44	6/44	5/41	1/23
Zymbal's gland				
Carcinoma, sebaceous/squamous cell	0/44	0/33	2/29	2/23
Female rats				
Liver				
Haemangiosarcoma	0/44	6/40	9/33	1/18
Adenoma, hepatocellular	0/44	3/40	4/33	5/18
Zymbal's gland				
Carcinoma, sebaceous/squamous cell	0/44	0/29	0/20	2/18

[a] Statistical evaluations were not performed due to variations in final euthanization dates among groups

***Table 5**: Summary of neoplastic observation in rats considering all time points.*

Tumour type	Tumour incidences/ number examined			
	Doses (ppm)			
	0	25	250	2500
Rats (Crl:CD®BR) : Males				
Liver				
Haemangiosarcoma	0/80	5/80 (6.25 %)	30/80 (37.5 %)	20/80 (25 %)
Hepatocellular adenoma	1/80 (1.25 %)	4/80 (5 %)	4/80 (5 %)	4/80 (5 %)
Hepatocellular carcinoma	4/80 (5 %)	6/80 (7.5 %)	6/80 (7.5 %)	3/80 (3.75 %)
Zymbal gland				
Carcinoma (sebaceous/squamous cell)	0/80	2/80 (2.5%)	3/80 (3.75%)	11/80 (13.75%)
Rats (Crl:CD®BR): Females				
Liver				
Haemangiosarcoma	0/80	8/80 (10 %)	19/80 (23.75 %)	15/80 (18.75 %)
Hepatocellular adenoma	0/80	4/80 (5 %)	9/80 (11.25 %)	5/80 (6.25 %)
Hepatocellular carcinoma	0/80	0/80	0/80	3/80 (3.75 %)
Zymbal gland				
Carcinoma (sebaceous/squamous cell)	0/80	0/80	1/80 (1.25%)	12/80 (15%)

Statistical analysis was not reported for the tumours when all time point sacrifices (0-24 months) were considered.

Hepatic haemangiosarcoma were reported by the DS to be the sentinel lesion in rats. The first appeared on test day 362 in female rats (2/18 at the 12 months interim sacrifice). At the 18 months interim sacrifice, incidences of liver haemangiosarcomas were concentration-dependently increased in male and female rats, reaching statistical significance at ≥250 ppm. When only considering the final sacrifice (Table 4) or considering all time points at once (Table 5), incidences of haemangiosarcomas showed a concentration-dependency at ≤250 ppm, but at the highest test concentration of 2500 ppm, incidences were lower than those reported for both sexes at 250 ppm. This finding, however, does not necessarily question a dose-dependency of the hepatic haemangiosarcoma incidence. RAC, in accordance with the DS, rather considers that this decrease in incidence at the highest test concentration may have been due to the excess early mortality that was observed particularly in this treatment group. Moreover, RAC notes that, despite the fact tht the footnote of Table 4 indicates that statistical analysis of the data at final sacrifice was performed, it becomes clear from the original publication that at the latest sacrifice (19-24 months), no statistics were performed by the study authors due to "to variations in final euthanisation dates among groups" (Bogdanffy et al, 1995). RAC considers that the lack of reported statistical significance at final sacrifice thus does not necessarily mean that there is in fact no statistical significance, and hence it also does not necessarily mean that there is no biological significance of this effect. Overall, RAC considers the observed increases in haemangiosarcoma incidences at each time point as relevant for humans.

Like the early appearance of haemangiosarcomas, incidence of sebaceous/squamous cell carcinoma in Zymbal's gland was increased at 2500 ppm already at the first interim sacrifice at 12 months after the start of the exposure (males: 4/17; females: 4/18) (Table 4). This effect, however, was reported to be only statistically significant in males at that time point and only in

females at the 18 months interim sacrifice (6/44; males at 18 months: 5/40), although neither control males nor control females showed this type of tumour at any of the analysed time points (Table 4). It is noted again that statistics were not performed at final sacrifice.

RAC further notes that Zymbal's gland was not collected as a target tissue and the reported tumours were observed as gross lesions. Thus, and since high early mortality was observed among exposed rats, the true incidence of this tumour type may be actually higher than the reported numbers.

RAC further notes that Zymbal's gland tumours are among those with no human equivalent, as reported in the CLP Guidance. However, the guidance also states: "Tumours occurring in such tissues indicate that the substance has the potential to induce carcinogenic effects in the species tested. It cannot automatically be ruled out that the substance could cause similar tumours of comparable cell/tissue origin (e.g. squamous cell tumours at other epithelial tissues) in humans. Careful consideration and expert judgement of these tumours in the context of the complete tumour response (i.e. if there are also tumours at other sites) and the assumed mode of action is required to decide if these findings would support a classification." In the scientific literature, moreover, CYP450 activity was noted in Zymbal's glands of rats and mice (Pohl et al, 1983) indicating that the reactive/genotoxic metabolites of fluoroethylene may be formed in this (and other) tissue(s), leading to tumour formation. As the available toxicokinetic data (as described in more detail in the section on toxicokinetics) suggests that the metabolites of fluoroethylene formed by CYP450 activity have a genotoxic mode of action, RAC considers the carcinoma of the Zymbal's gland observed in treated rats to be relevant for humans.

Hepatocellular carcinomas were first seen in one male rat at the 12 months interim sacrifice. At the later analysed time points, statistically non-significant increased incidences of this tumour type (adenoma and carcinoma) were generally noted in all treatment groups compared to the controls, but a clear concentration-dependency was lacking at the single sacrifices. Overall and when combining the incidences of hepatocellular adenomas and carcinomas, a dose-dependent increase was noted at ≤250 ppm, but not at the high concentration of 2500 ppm. Again, this may have been due to the excess early mortality in all dose groups, but particularly at the highest test concentration (Figure 2**Error! Reference source not found.**). Although statistical significance was lacking, the decreased tumour latency, increased multiplicity, and associated increases in potentially pre-neoplastic basophilic foci lead to the conclusion that the observed benign and malignant tumours were related to test substance exposure. Overall, RAC considers these increases in tumour incidence of relevance for humans.

The DS reported that additional examination of cell proliferation using BrdU staining was performed in 5 rats/group at sacrifices at approximately 2 weeks, 3 months, and 12 months of exposure. These studies were conducted as an adjunct to the core oncogenicity study (Bogdanffy et al, 1990). There was no change in mean final body weight or mean final absolute or relative organ weight attributable to fluoroethylene exposure at any of the 3 euthanisation time points. The only compound-related lesions of significance noted at these sacrifices were noted at the 12-month euthanasia and included a hepatic haemangiosarcoma in male rats exposed to 2500 ppm fluoroethylene and increased incidences of basophilic, eosinophilic or clear cell foci in liver of animals of all dose groups. 2/5 female rats at 250 ppm had mixed foci of cellular alteration. No impact of fluoroethylene exposure on cell proliferation was detected in the analysed organs and tissues (liver, lung, nose and kidneys). This contrasts with the results of a previous 90-day study in which significant increases were noted at concentrations equals to or greater than 200 ppm (Bogdanffy et al, 1990).

Under the conditions of this study, the substance was carcinogenic in male and female rats at concentrations greater than or equal to the lowest test concentration of 25 ppm (= LOAEC;

corresponding to 47 mg/m³). A no-observable adverse effect level (NOAEL) was, thus, not determinable.

Mouse study (Anonymous,1992; Bogdanffy *et al*,1995)

Groups of 95 male and 95 female Crl:CD®-l(ICR)BR mice were exposed to either 0, 25, 250, or 2500 ppm test substance for 6 hours per day, 5 days per week, for up to 18 months, weekends and holidays excluded.

Benign and malignant tumours in different tissues of mice were observed at the interim sacrifices after 6 months of exposure, and at the final sacrifice at 18 months.

As well as in the rat study, early mortality was also observed in the mouse study. In this study, however, more than 50% of control animals survived until study termination, indicating that the study can be considered reliable by OECD- (TG 453) and US-EPA- (EPA OTS 798.3300) standards. Mortality was particularly high at ≥ 250 ppm and subsequent to the first 6 months of exposure (3). Because of the high mortality, animals exposed to 250 ppm were killed between day 412-459 and animals exposed to 2500 ppm between day 375-450. There were no clinical observations specifically associated with the early deaths, mortality in all exposed animals was sudden and without clinical observations associated with morbidity. Female mice of the exposed groups had higher incidences of masses compared to controls: increased incidence of mammary gland neoplasms, primarily adenocarcinomas, were present in all treated groups of female mice. There was a statistically significant decrease in survival among male mice of the 250 and 2500 ppm groups compared to controls and of female mice at 25 ppm compared to controls. Mortality was reported to be primarily due to test substance-induced haemorrhage from haemangiosarcomas. Overall, incidences of male mice of the 0, 25, 250, and 2500 ppm groups with haemorrhage from haemangiosarcoma assigned as the cause of death were 0/81, 20/80, 33/80, and 37/81, respectively. The incidences in female mice were 1/81, 22/81, 30/80, and 30/81, respectively. A non-significant increased incidence of hepatocellular adenomas was present in 25 ppm males (11/80 versus 6/81 in the control group However, the decreased tumour latency, increased multiplicity, and associated increase in putatively preneoplastic basophilic foci led to the conclusion that the tumours were related to test substance exposure. Mammary gland neoplasms were also a cause of death among exposed female mice with 0/81, 10/81, 11/80, and 10/81 females dying from mammary gland neoplasms at 0, 25, 250, and 2500 ppm, respectively.

Besides the high mortality, other than sporadic differences of statistical significance only, mean body weight was not statistically significantly affected by fluoroethylene inhalation exposure. Mean body weight gain of male mice at 2500 ppm, however, was significantly decreased (-17%) relative to controls over the 1-372 day interval. Mean body weight gain of mice in the remaining exposure groups was similar to controls, indicating that mortality was probably not due to excessive toxicity at the tested concentrations.

At necropsy, the following main gross observations were related to test substance exposure: nodules, masses and discoloration of the lung, and fluid in the pleural cavity; masses of the peritoneal cavity and haemorrhage, cysts, masses, discoloration and nodules of the liver; and mammary gland masses. Non-neoplastic lesions, which were considered precursors to test substance-induced neoplasms were bronchioloalveolar hyperplasia in the lung, hypertrophy/hyperplasia/angiectasis and basophilic foci in the liver (in males at 25 ppm) mammary gland hyperplasia, and acinar hypertrophy/hyperplasia in the Harderian gland.

Microscopically, these lesions were correlated with bronchioloalveolar adenoma, hepatic haemangiosarcoma and mammary gland adenocarcinoma. The incidences of these lesions were concentration-related in all exposed groups (Table 6).

***Table 6**: Neoplastic microscopic observations in target organs of male and female mice necropsied during a) 0-6 months and b) 7-18 months[a].*

a)

0-6 months	**Concentrations**			
Dose (ppm):	0	25	250	2500
Male mice				
Lungs				
Adenoma, bronchioloalveolar	**0/14**	**2/11**	**4*/14**	**7*/18**
Hyperplasia, bronchioloalveolar	**0/14**	**0/11**	**0/14**	**6*/18**
Liver				
Haemangiosarcoma	0/14	0/11	0/14	1/18
Female mice				
Lungs				
Adenoma, bronchioloalveolar	**0/17**	**2/20**	**1/13**	**4*/15**
Hyperplasia	**0/17**	**0/20**	**0/13**	**2*/15**

b)

7-18 months	**Concentrations**			
Dose (ppm):	0	25	250	2500
Male mice				
Lungs				
Hyperplasia, bronchioloalveolar	2/67	17/69	26/66	34/63
Adenoma, bronchioloalveolar	11/67	43/69	48/66	49/63
Adenocarcinoma, bronchioloalveolar	1/67	1/69	4/66	4/63
Liver				
Haemangiosarcoma	1/67	16/69	42/66	41/63
Adenoma, hepatocellular	7/67	15/69	5/66	3/63
Carcinoma, hepatocellular	2/67	2/69	1/66	0/63
Harderian gland				
Adenoma	3/66	13/69	12/66	31/62
Female mice				
Lungs				
Hyperplasia, bronchioloalveolar	1/64	5/60	27/67	34/66
Adenoma, bronchioloalveolar	9/64	22/60	46/67	49/66
Adenocarcinoma, bronchioloalveolar	0/64	1/60	1/67	3/66
Liver				
Adenoma, hepatocellular	0/64	0/61	1/67	0/66
Haemangiosarcoma	0/64	13/61	25/67	32/66
Mammary gland				
Hyperplasia	1/62	14/60	17/65	14/64
Adenoma	0/62	0/60	0/65	1/64
Fibroadenoma	0/62	0/60	0/65	2/64
Adenocarcinoma	0/62	22/60	20/65	19/64
Harderian gland				
Adenoma	1/64	7/61	6/66	12/66

[a] Statistical evaluations were not performed due to variations in final euthanization dates among groups

Bronchioloalveolar adenomas appeared to be the sentinel lesion in mice, as the first appeared early, already on test day 89, indicating a reduced tumour latency. In males the incidence of this tumour type was statistically significantly increased at ≥ 250 ppm at the interim sacrifice, 6 months after the exposure start (Table 6a). In females, this increase was only statistically significant at the high concentration of 2500 ppm. Hyperplasia in the lungs of male and female mice was reported only at the highest test concentration at the 6 months assessment time point.

At the final sacrifice after 18 months of exposure, bronchoalveolar hyperplasia and adenoma were clearly and dose-dependently increased in male and female mice. Bronchoalveolar adenocarcinoma were increased in treated male and female lungs with the highest incidence at the highest test concentration (6% in males vs. 0% in control males; 4.5% in females versus 0% in control females). No statistical significance was assigned to these high incidences, despite the lack of these tumours in control animals (Table 6b). As in the rat study, the footnote of Table 6 indicates that statistical analysis of the data was performed. However, having a closer look at the scientific publication, it becomes clear that at the later time point (i.e. after 18 months), no statistics were performed by the study authors due to "to variations in final euthanisation dates among groups" (Bogdanffy et al, 1995), as it was the case in the rat study. Thus, the lack of reported statistical significance does not necessarily mean that there is in fact no statistical significance and it also does not necessarily mean that there is no biological significance of this effect. Unfortunately, as no specific data regarding the individual time points of mortality/sacrifices and concurrent histopathological findings are reported, RAC retrospectively cannot perform correct and conclusive statistical analyses based on the available data.

Similarly to the benign bronchoalveolar tumours, the first hepatic haemangiosarcoma appeared already on test day 162 in one male mouse at 2500 ppm (Table 6a). Incidences of the malignant haemangiosarcomas were visibly and concentration-dependently increased in treated male and female mice at final sacrifice, but again no statistical significance was reported (as not tested). At the highest test concentration after 18 months of exposure, incidence of haemangiosarcomas was 65% in males versus 1.5% in control males. In females, the incidence of this tumour type was 48.5% at 2500 ppm after 18 months versus 0% in controls.

In addition to the tumours in the lungs and liver, Harderian gland adenomas were observed at a higher incidence in treated versus controls male and female mice, but statistical analyses were again not performed (at 2500 ppm: 50% of males versus 4.5% control males and 18.2% of females versus 1.6% of control females; Table 6b).

In females, moreover, increases in incidences of hyperplasia, adenoma, fibroadenoma and adenocarcinoma in mammary gland were reported (Table 6b). Incidences of adenocarcinomas were generally high at final sacrifice (i.e. ≥30% in each of the 3 treatment groups versus 0% in control females), but did not follow a clear concentration-dependency.

Extrahepatic haemangiosarcomas and haemangiomas in the peritoneum, mammary glands, ovaries, and epididymides (at 25 ppm only, without dose-response relationship) occurred only with lower frequency and increased latency relative to the tumours in the liver (Table 7 and Table 8).

***Table 7**: Incidences of extrahepatic haemangiosarcomas in male mice.*

Group:	**I**	**III**	**V**	**VII**
Dose (ppm):	0	25	250	2500
Other Tissues with Haemangiosarcoma – Malignant (Primary)[c]				
Spleen	0	1	0	1
Epididymides	0	7	0	0
Skeletal Muscle	0	1	0	0
Peritoneum	0	9	5	1
Blood Vessels – Liver/ Peritoneum	0	1	1	1

[c] Only tissues with haemangiosarcoma observed in the 25 ppm group are listed. Haemangiosarcoma was observed in other tissues in the higher concentration groups.

***Table 8**: Incidences of extrahepatic haemangiosarcomas in female mice*.

Group:	**I**	**III**	**V**	**VII**
Dose (ppm):	0	25	250	2500
Other Tissues with Haemangiosarcoma – Malignant (Primary)[d]				
Cecum	0	1	0	0
Urinary Bladder	0	1	0	0
Uterus	0	2	1	2
Mammary Gland	0	2	0	1
Skeletal Muscle	0	1	0	0
Peritoneum	0	19	11	7
Pleura	0	1	0	0

[d] Only tissues with haemangiosarcoma observed in the 25 ppm group are listed. Haemangiosarcoma was observed in other tissues in the higher concentration groups.

Combining the findings of both, the interim and the final sacrifice (Table 9), bronchoalveolar adenoma were found in over 60% of male and female mice of the high-concentration group, while only <14% of control animals showed this effect. Similarly, incidences of haemangiosarcomas were found in 52% of males and 40% of female mice at 2500 ppm versus 1.2% and 0% in control males and females, respectively. Harderian gland adenoma were found with one order of magnitude higher incidences at 2500 ppm fluoroethylene than in concurrent controls. And while no adverse effects were detected in male mammary glands, more than 25% of treated females (at each of the 3 test concentrations) had adenomas, adenocarcinomas or fibroadenomas (combined) versus 0% in controls. Regarding the tumours in female mammary glands, however, no clear dose-dependency in tumour development could be detected.

Table 9: *Summary of neoplastic observation in mice*

Tumour type	**Tumour incidences/ number examined**			
	Doses (ppm)			
	0	**25**	**250**	**2500**
Mice (Crl:CD®-1(ICR)BR): males				
Lungs				
Primary lung tumours	11/81 (13.58 %)	45/80 (56.25 %)	52/80 (65 %)	56/81 (70 %)
Bronchioalveolar adenoma	11/81(13.58 %)	43/80 (53.75 %)	48/80 (60 %)	49/81 (60.49 %)
Bronchioalveolar adenocarcinoma	1/81 (1.23 %)	1/81 (1.25 %)	4/80 (5.0 %)	4/81 (5.0 %)
Liver				
Haemangiosarcoma	1/81 (1.23 %)	16/80 (20 %)	42/80 (52.5 %)	42/81 (51.8 %)
Hepatocellular adenoma	7/81 (8.64 %)	15/80 (18.75 %)	5/80 (6.25 %)	3/81 (3.7 %)
Hepatocellular carcinoma	2/81 (2.47 %)	2/80 (2.5 %)	1/80 (1.25 %)	0/81
Harderian gland adeno	3/80 (3.75%)	13/79 (16.45%)	12/80 (15%)	31/80 (38.75%)
Tumour type	**Tumour incidences/ number examined**			
	Doses (ppm)			
	0	**25**	**250**	**2500**
Mice (Crl:CD®-1(ICR)BR) : females				
Lungs				
Primary lung tumours	9/81 (11.11 %)	24/80 (30 %)	47/80 (58.75 %)	53/81 (65.43 %)
Bronchioalveolar adenoma	9/81 (11.11 %)	22/80 (27.5 %)	46/80 (57.5 %)	49/81 (60.49 %)
Bronchioalveolar adenocarcinoma	0/81	1/80 (1.25 %)	1/80 (1.25 %)	3/81 (3.7 %)
Liver				
Haemangiosarcoma	0/81	13/81 (16.04 %)	25/80 (31.25 %)	32/81 (39.50 %)
Hepatocellular adenoma	0/81	0/81	1/80 (1.25 %)	0/81
Mammary gland				
Adenoma	0/79	0/80	0/78	1/79 (1.26 %)
Adenocarcinoma	0/79	22/80 (27.5 %)	20/78 (25.6 %)	19/79 (24 %)
Adenoma, adenocarcinoma, fibroadenoma (combined)	0/77	22/76 (28.9%)	20/78 (25.6 %)	20/77 (25.97%)
Harderian gland adenoma	1/81 (1.23%)	7/81 (8.64%)	6/79 (7.59%)	12/81 (14.81%)

Statistical analysis was not reported for the tumours when all time point sacrifices (0-24 months) were considered.

In the organs examined by the study authors, there were no increases in cell proliferation that were consistent and could be related to the test substance exposure. Mild increases in cell proliferation were noted in the liver of male mice but large standard deviations precluded meaningful conclusions.

It was noted, however, that the spectrum of test substance-induced tumours is similar to that induced by other similar test substances in mice.

Overall, under the conditions of this study, the test substance was carcinogenic in male and female mice at ≥25 ppm. No NOAEL was determinable, as the LOAEL was the lowest tested concentration.

Legal framework for weight of evidence and the carcinogenicity classification

According to Article 9(3) of the CLP Regulation, where classification criteria cannot be applied directly to available identified information, the weight of evidence determination using expert judgment shall be carried out, weighing all available information having a bearing on the determination of the hazards of the substance or the mixture.

The weight of evidence determination is defined in Section 1.1.1.3 of Annex to the CLP Regulation: *"A weight of evidence determination means that all available information bearing on the determination of hazard is considered together, such as the results of suitable in vitro tests, relevant animal data, information from the application of the category approach (grouping, read-across), (Q)SAR results, human experience such as occupational data and data from accident databases, epidemiological and clinical studies and well-documented case reports and observations. The quality and consistency of the data shall be given appropriate weight. Information on substances or mixtures related to the substance or mixture being classified shall be considered as appropriate, as well as site of action and mechanism or mode of action study results. Both positive and negative results shall be assembled together in a single weight of evidence determination."*

According to section 3.6.2.2.1 of Annex I to , the classification of substances as carcinogens shall be based on all existing data. Section 3.6.2.1 of Annex I provides that for the purposes of classification substances are assigned to one of the two categories of classification (Category 1A/1B or Category 2) according to their carcinogenic effect "*on the basis of the strength of the evidence and additional considerations (weight of evidence)*"

Similarly, according to section 3.6.2.2.2., the classification of a substance as a carcinogen is a process that involves two interrelated determinations, evaluations of strength of evidence in animals and consideration of all other relevant information to place substances with human cancer potential into the following hazard categories:

Category 1 (Known or presumed human carcinogens) for substances, for which there is evidence largely based on human evidence (Cat. 1A) or for which there is evidence largely based on animal evidence mainly coming from animal studies (Cat. 1B). In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals.

Category 2 (Suspected human carcinogens) for substances, for which the basis of evidence is obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B, based on strength of evidence together with additional

considerations. Such evidence may be derived either from limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.

The CLP Regulation further states in Section 3.6.2.2.7. of Annex I: *"A substance that has not been tested for carcinogenicity may in certain instances be classified in Category 1A, Category 1B or Category 2 based on tumour data from a structural analogue together with substantial support from consideration of other important factors such as formation of common significant metabolites, e.g. for benzidine congener dyes."*

RAC conclusion on classification and labelling of fluoroethylene based on the available data on the substance itself

To assess the carcinogenicity of fluoroethylene, guideline- and GLP-compliant carcinogenicity studies in rats and mice, respectively, are available. RAC agrees with the DS and the evaluation by the IARC (2008) that in the available studies, a causal relationship between exposure to fluoroethylene and an increased incidence of malignant neoplasms in two species and two sexes has been established. (IARC conclusion: "There is sufficient evidence in experimental animals for the carcinogenicity of vinyl fluoride" [fluoroethylene].)

Table 10: Uncertainty analysis of factors increasing or decreasing the level of concern for human carcinogenicity (Section 3.6.2.2.6, Annex I: CLP Regulation)

Species and strain	**Tumour type and background incidence**	**Multi-site responses**	**Progression to malignancy**	**Reduced tumour latency**	**Responses in single or both sexes**	**Confounding effect/ excessive toxicity?**	**Route of exposure**	**MoA and relevance to humans***
Rats Crl:CD®BR	Liver: haemangiosarcomas (rare tumour type) and hepatocellular adenomas/ carcinomas	Yes, concern increased	Yes, concern increased	No informa-tion	Males and females (haemangio-sarcomas, hepato-cellular adenoma/ carcinoma in females only)	Cannot be excluded, albeit unlikely (high mortality occurred at tested doses, as well as in controls. Increases in tumour incidences are considered clearly substance-related.)	Inhalation (data for other routes not available)	Relevant for humans (concern increased)
	Zymbal gland: sebaceous/ squamous cell carcinoma			No informa-tion	Males and females			No equivalent organ in humans, but considered relevant for humans due to MoA

Species and strain	Tumour type and background incidence	Multi-site responses	Progression to malignancy	Reduced tumour latency	Responses in single or both sexes	Confounding effect/ excessive toxicity?	Route of exposure	MoA and relevance to humans*
Mice Crl:CD®-1(ICR)BR	Liver: haemangiosarcoma (rare tumour type) and hepatocellular adenoma	Yes, concern increased	Yes, concern increased	No informat-ion	Males and females	No (rather high mortality occurred, particularly at the 2 highest tested doses but not in controls).	Inhalation (data for other routes not available)	Relevant for humans
	Lungs: Bronchioalveolar adenoma		No	Yes (first appearance on day 89)	Males and females			Relevant for humans
	Harderian-gland: adenoma		No	No information	Males and females			Not relevant for humans
	Mammary-gland: adenocarcinoma		Yes, concern increased	No information	Females only			Relevant for humans
	Extrahepatic: haemangiosarcoma and haemangioma (malignant)		Yes, concern increased	No information	Females (peritoneum, mammary gland, ovaries) and males (epididymis, peritoneum)	No (only observed at 25 ppm)		Relevant for humans

* Metabolism hypothesis and mutagenicity results suggest that the carcinogenicity of the substance is at least partially mediated via a genotoxic MoA.

Several different malignant tumour types were observed in two different species (rats and mice) and in two sexes significantly increasing the concern regarding the carcinogenicity of fluoroethylene. In addition, hepatocellular foci that may represent pre-neoplastic effects were also seen in the available carcinogenicity studies with rats and mice, as well as in a sub-chronic study with new-born rats (Bolt *et al*, 1981). All of the tumour types observed in the chronic studies are considered relevant for humans and the underlying mode of action is assumed to be due to the formation of reactive/genotoxic metabolites of the substance via CYP2E1. Metabolism and toxicity of fluoroethylene is considered similar in rats, mice and humans.

In the carcinogenicity study in rats, very high mortality was observed, particularly in the two higher dose groups, although no statistically significant effects on body weight were noted, which may indicate an excess toxicity of the test substance at those test concentrations. Moreover, mortality was also high in control rats, suggesting a general excess mortality independent of the fluoroethylene treatments. Although, this high general mortality observed in the rat study increases the uncertainties regarding the study reliability and thus regarding the relevance of the observed increases in tumour incidences in rats, RAC overall considers the reported increases in tumour incidences in rats as clearly substance-related. This conclusion is particularly based on the remarkable dose-related increases in incidences of hepatic haemangiosarcomas in both sexes. Hepatic haemangiosarcoma is a rather rare tumour type in SD-rats, particularly rare in female SD-rats (Giknis *et al*, 2004 and 2013). In addition, this type of tumour was not only observed in male and female rats, but also in male and female mice. In the mouse study, mortality of control animals was below 50%. The study is thus considered fully reliable. Furthermore,

haemangiosarcoma and hepatic haemangiosarcoma is also a rare tumour type in CD1-mice (Maita *et al*, 1988, Chandra and Frith, 1992). Hence, the similarity in tumorigenic findings (i.e. the haemangiosarcomas) observed in the liver of both species and in both sexes decreases the concern regarding the uncertainties with respect to the reliability of the rat study results.

No historical control data (HCD) are available for the two reported studies, increasing the uncertainty regarding the relevance of the malignant findings. However, due to the fact that remarkable increases in malignant tumour incidences, particularly the increase in the incidence of identical tumour type, hepatic haemangiosarcoma, were found in two species and two sexes, this uncertainty can be regarded as rather low. The low-to-absent incidence of the malignant tumour type in the concurrent control groups (Table 5 and Table 9) further diminish the uncertainties with regards to the reliability and relevance of the study results. In addition, historic control data from other laboratories indicate that for SD-rats and CD-1 mice, background incidences of hepatic haemangiosarcomas are rather low.

Metastatic spread of tumours was not reported, but tumours – particularly the hepatic haemangiosarcomas and mammary gland adenocarcinomas were frequently listed as the cause of death.

Taking into consideration the animal data on fluoroethylene alone, RAC considers that there is sufficient evidence to demonstrate animal carcinogenicity of fluoroethylene justifying classification for carcinogenicity, Category 1B, H350 (May cause cancer).

Moreover, the DS used data on the analogue substance chloroethylene for justifying classification of fluoroethylene as Carc. 1A, H350. The conclusion of RAC on the applied read-across and subsequent classification of fluoroethylene can be found in the next section.

RAC assessment of the proposed read-across

The DS used data on the analogue substance chloroethylene (and partly also bromoethylene) for justifying classification of fluoroethylene as Carc. 1A, H350.

The US EPA OncoLogic Cancer Expert System (version 7.0) for predicting carcinogenic potential indicated an endpoint-specific structural alert for carcinogenicity ("Oncologic primary classification C-Nitroso and Oxime Type") for all three substances.

RAC agrees with the DS that fluoroethylene, chloroethylene and bromoethylene are structurally very similar, as all they only differ with respect to the halogen substituent (F, Cl or Br). Each halogen is considered to produce a similar donor mesomeric effect on the double bond, which renders the substance reactive.

The DS further proposes that based on their physico-chemical properties, they may elicit similar biological effects. However, RAC notes that although structural similarity is strong, there are some differences in some of the important physico-chemical properties of fluoroethylene and the 2 other haloethylenes (e.g. vapour pressure, boiling point, solubility; Table 3).

Nevertheless, several studies are available investigating the toxicokinetics/pharmacokinetics of the three haloethylenes (summarised in IARC, 2008). In these studies, it was shown that pharmacokinetics and metabolism of the three haloethylenes are similar (IARC 2008). The initial oxidation of the three haloethylenes results in the formation of haloethylene oxides (epoxides) and is mediated by cytochrome CYP2E1. Haloethylene oxides are then re-arranged to haloacetaldehydes. As with chloroethylene, metabolism of bromoethylene and fluoroethylene is a saturable process, meaning that an increase in atmospheric concentrations of these substances does not similarly enhance the hepatic tumour rate, as this is dependent on metabolite formation and subsequent metabolite action. Older pharmacokinetic data also indicate that fluoroethylene is metabolised faster than bromoethylene, but slower than chloroethylene. However, furthermore recent toxicokinetic data suggests that metabolism rates of bromoethylene and chloroethylene

are in a similar range, e.g. when tested in human liver microsomes of 11 individuals *in vitro* (Guengerich *et al*, 1991). Testing both substances *in vitro* in purified human liver CYP2E1 obtained from only one individual resulted in identical metabolism rates demonstrating that there may not be any differences in metabolism rates of the haloethylenes at the individual level. Unfortunately, data on fluoroethylene metabolism rates are not available. In contrast to experimental animal models, humans show large inter-individual variations in CYP-catalysed oxidation reactions of drugs and chemicals, leading to generally large inter-individual differences in toxicity of CYP2E1 substrates (Bolt *et al*, 2002). Inter-individual and inter-ethnic variability in the expression of isozyme CYP2E1 in humans were predicted to be most likely the key factors in predicting fluoroethylene/chloroethylene/bromoethylene metabolic capability and susceptibility towards tumour formation (Cantoreggi *et al*, 1997).

Despite of the rates of metabolism, the formed metabolites of all three haloethylenes (epoxides and acetaldehydes) were shown to be able to bind with proteins, DNA and RNA and form etheno-adducts, which may be responsible for the mutagenesis and carcinogenicity of fluoroethylene and chloroethylene (IARC, 2008). Detoxification of reactive metabolites occurs via microsomal epoxide-hydrolases and aldehyde dehydrogenases, respectively (IARC, 2008).

RAC agrees that the available toxicokinetics/pharmacokinetics data on the three haloethylenes support a possible read-across between the substances.

RAC further considers the available toxicity data for the source substances bromoethylene, but particularly the data on chloroethylene as relevant and reliable for the purpose of read-across.

Fluoroethylene is considered a genotoxicant in somatic cells (see section on germ cell mutagenicity). Fluoroethylene metabolites form covalent DNA adducts that are similar to those formed by metabolites of chloroethylene and bromoethylene (IARC, 2008). These include N7-(2′ -oxoethyl)guanine (7-OEG), N7-(2′ -oxoethyl)guanosine, and N2,3-ethenoguanine (N2,3-εG), 1,N 6-ethenoadenine and 3,N 4-ethenocytosine. Target cell populations for angiosarcomas in fluoroethylene-exposed rats are non-parenchymal cells, which contain more N2,3-εG than hepatocytes and have lower expression of the associated DNA-repair enzyme N-methylpurine–DNA glycosylase. Other fluoroethylene-induced DNA adducts were not measured in these animals. Formation of these pro-mutagenic adducts may be implicated in the mutagenicity and carcinogenicity of fluoroethylene as it is suggested for chloroethylene (IARC, 2008).

Information reviewed by IARC (2008) points towards similar mutagenic effects as those reported for fluoroethylene, as chloroethylene was shown to induce gene mutations *in vitro* and DNA strand breaks, sister chromatid exchange, micronucleus formation and chromosomal aberrations in rodents *in vivo*. *In vitro*, a higher mutagenic response was obtained in the presence of an exogenous metabolic activation system from rat liver, supporting the proposed mode of action via the formation of genotoxic metabolites. Bromoethylene similarly induced gene mutations *in vitro*, and yielded positive results in the stomach, liver, kidney, bladder, lung and brain, but not in bone marrow of male CD-1 mice in an *in vivo* comet assay (IARC 2008).

Chloroethylene and bromoethylene have no harmonised classification for their mutagenicity properties and their harmonised classification for carcinogenicity predates the CLP Regulation. Some of the self-classifications notified under CLP for chloroethylene (but not bromoethylene) include a Muta. 2 classification.

In the available carcinogenicity studies with the three haloethylenes, the purity profiles are reported to be high (≥99%) (IARC, 2008).

Bromoethylene was tested in female mice by skin application and by subcutaneous injection, and in rats by inhalation exposure (IARC, 2008). No skin tumours were found after chronic dermal application of bromoethylene in mice. Similarly, no skin tumours were detected after 48-weeks

of subcutaneous injections in mice (observation period: 480 days). Systemic carcinogenicity was not assessed in any of these studies.

Similarly to the findings after chronic inhalation exposure to fluoroethylene, dose-related increases in the incidence of liver angiosarcomas and Zymbal gland carcinomas in male and female rats were observed in the chronic inhalation study with bromoethylene in rats. An increased incidence of hepatic neoplastic nodules and hepatocellular carcinoma was also noted (IARC, 2008), but – as with fluoroethylene and possibly due to haemangiosarcoma-related unscheduled deaths – the increases did not show a clear concentration-dependence.

For chloroethylene, available chronic studies (summarised in IARC, 2008) in rats and mice show that long-term inhalation and chronic oral administration of this substance induces cancer in both species and both sexes at multiple sites. Tumours included the identical tumour types as after chronic fluoroethylene inhalation: angiosarcomas at many sites (but predominantly haemangiosarcoma in liver), hepatocellular tumours, tumours of the mammary, and lung tumours. Tumour incidences increased dose-dependently and were generally high (and accompanied by benign (pre-neoplastic) lesions, e.g. in the liver). In a perinatal rat study, in which breeder pairs were exposed via inhalation together with their offspring, perinatal exposure for 5 weeks also resulted in remarkable increases in hepatic angiosarcomas, angiomas and 'hepatomas', as well as in Zymbal gland carcinomas and mammary tumours in exposed offspring. For chloroethylene also chronic studies in hamster are available, a species that was neither tested in studies with fluoroethylene nor with bromoethylene. Besides hepatic haemangiosarcomas and mammary gland carcinomas, additional tumour types were observed in the hamsters after chronic inhalation of chloroethylene, which were not reported for rats and mice, namely skin tumours, leukaemia and tumours of the glandular stomach. In (sub-)chronic repeated dose inhalation studies with chloroethylene liver foci of cellular alterations, that may represent pre-neoplastic lesions, were also noted in different sexes and species.[1]

Overall and when comparing the respective data obtained after chronic fluoroethylene, chloroethylene and bromoethylene exposure in test animals, it becomes clear that fluoroethylene, as the two other known carcinogens, has an oncogenic potential, particularly in the liver of the animals (i.e. induces haemangiosarcomas in mice and rats and in both sexes). The mode of action of all three substances is considered to be mediated via genotoxic metabolites of the haloethylenes formed by activation via CYP450 (CYP2E1).

Based on these consistent findings regarding metabolism and similar metabolite formation via CYP2E1, the likely genotoxic mode of action of the formed metabolites of the three haloethylenes, as well as the similar patterns in carcinogenicity with all three substances, RAC considers the

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[1] rabbits:
https://echa.europa.eu/de/registration-dossier/-/registered-dossier/16163/7/6/3/?documentUUID=82d96a6f-feef-4204-bef9-8c8f436793e9);

rats:

https://echa.europa.eu/de/registration-dossier/-/registered-dossier/16163/7/6/3/?documentUUID=eb6d265a-85f1-45af-815c-0b40de48d181,

https://echa.europa.eu/de/registration-dossier/-/registered-dossier/16163/7/6/3/?documentUUID=843d44de-e9ae-4f39-873b-ce2c836fd815 , https://echa.europa.eu/de/registration-dossier/-/registered-dossier/16163/7/6/3/?documentUUID=802b2149-eb22-4f3e-8ec1-062c260211d8,

https://echa.europa.eu/de/registration-dossier/-/registered-dossier/16163/7/6/3/?documentUUID=a0d95fa8-ba3f-4674-9cae-e4e066180916) .

uncertainties regarding the use of chloroethylene and bromoethylene as source substances in a read-across approach for the target substance fluoroethylene as rather low. Overall, RAC considers a read-across approach for fluoroethylene from the source substances chloroethylene and bromoethylene as acceptable.

For chloroethylene, additional human evidence is available that justifies its harmonised classification for Carc. 1A, H350.

Besides several case reports with workers in the manufacture of PVC resins, which provided the first evidence of an association between chloroethylene and cancer (i.e. angiosarcomas of the liver) in humans, further evidence comes from two large epidemiological cohort studies of workers exposed to chloroethylene (in the manufacturing of chloroethylene monomers). One study was carried out in the US and one in Europe. In these studies, the occurrence of liver cirrhosis and liver cancer, particularly hepatic angiosarcomas, and subsequent increased mortality was significantly associated with exposure to chloroethylene (IARC, 2008). In addition, multiple smaller cohort studies are reported in the IARC monograph (2008), similarly associating exposure to chloroethylene with liver cancer in workers (in most studies specified as angiosarcomas of the liver, some not specified).

In addition, several epidemiological studies showed a moderate association of exposure to chloroethylene with cancers of the brain or lymphatic and hematopoietic tissue or melanoma. Although the associations found for these cancers in specific studies may reflect true increases in risk, the findings were inconsistent between studies, no clear exposure–response relationships were found in the European multicentre study and, for several of the sites, the numbers of observed and expected cases were small.

In a meta-analysis of the available data, the IARC (2008) found that in approximately half of the (haem)angiosarcomas observed in humans (analyses in several of the available human studies) and rats a mutated p53 gene was found that resulted from exposure to chloroethylene. The p53 mutations in both species were often due to A→T transversions (Hollstein *et al*, 1994; Barbin *et al*, 1997; reviewed in IARC, 2008). These results further support the similarity of tumour type, tumour pattern and mode of action of tumour formation in humans and animals. Thus overall, epidemiological studies of occupational exposure have shown that chloroethylene causes cancer of the liver blood vessels (hepatic angiosarcoma) in humans (IARC 2008), a tumour that is extremely rare in the general population. In experimental animals, this type of cancer is usually referred to as haemangiosarcoma.

Based on these study results, the IARC (2008) concluded that "there is sufficient evidence in humans for the carcinogenicity of vinyl chloride [chloroethylene]. Vinyl chloride causes angiosarcomas of the liver and hepatocellular carcinomas" and that "Vinyl chloride is carcinogenic to humans (Group 1)".

Overall and due to the similarities in metabolism, toxicity, mode of action and pattern in carcinogenicity, the DS concluded that fluoroethylene and bromoethylene – like chloroethylene – can elicit tumourigenic effects in humans as well, although epidemiological evidence is lacking for the two substances. (For information: Bromoethylene is classified as Carcinogenic, Cat. 1B. Its carcinogenic potential has not been re-assessed and the classification has not been updated since the introduction of the CLP Regulation.)

RAC finds that the angiosarcomas, the predominant tumour type observed in epidemiological studies in workers exposed to chloroethylene, corresponded to the haemangiosarcomas observed in animal cancer studies on fluoroethylene, bromoethylene and chloroethylene (see Table 11). A comparison of the percentages of haemangiosarcomas in rats at the equimolar dose of 250 ppm (a dose tested in rat cancer studies for all three compounds and at which tumour-related early deaths did not hamper the assessment) indicates that bromoethylene and fluoroethylene are expected to similarly exert a high or even higher carcinogenic potency than chloroethylene.

Maximum percentages of haemangiosarcoma incidences in rats were 51% (bromoethylene, males and females), 38% (fluoroethylene, males) and 29% (chloroethylene, females) (Benya *et al*, 1982; Bogdanffy *et al*, 1995; Lee *et al*, 1978; all cited in IARC, 2008). Due to the high mortality at the higher doses in the available carcinogenicity studies, a reliable dose-response-relationship (and a BMDL) calculation for direct comparison of the carcinogenic potency of the three substances is considered not possible.

Table 11: *Summary of cancer types (reported in experimental studies with fluoroethylene, chloroethylene or bromoethylene via the inhalation route (modified from Table 18 of the CLH dossier; data summarised from Anonymous (1992); Bogdanffy et al, (1995); IARC (2008)).*

Cancers	Fluoroethylene	Vinyl chloride	Vinyl bromide
Hepatic angiosarcomas *	Rats (1 study)/ Mice (1 study)	Mice (2 studies) / Rats (9 studies) / Hamsters (1 study)	Rats (1 study)
Extrahepatic angiosarcomas *	Mice (1 study)	Mice (3 studies) / Rats (5 studies)	Rats (1 study)
Haemangiosarcomas * (liver)	Rats (1 study)/ Mice (1 study)	Mice (1 studies) / Rats (2 studies)	Rats (1 study)
Haemangiosarcomas * (all sites)	Mice (1 study)	Mice (2 studies) / Rats (2 studies) / Hamster (1 study)	Rats (1 study)
Hepatocellular carcinomas or adenomas	Rats (1 study)/ Mice (1 study)	Rats (1 studies)	Rats (1 study)
Zymbal gland carcinomas	Rats (1 study)	Rats (5 studies)	Rats (1 study)
Mammary gland tumours	Mice (1 study)	Mice (6 studies), Rats (3 studies), Hamsters (1 study)	
Lung tumours	Mice (1 study)	Mice (6/7 studies with Swiss-CD1, a strain that is more susceptible to the induction of lung tumours)	
Skin tumours		Rats (1 study), Mice (1 study), Hamsters (2 studies)	
Tumours of the nasal cavity		Rats (1 study)	
Glandular stomach tumours		Hamster (2 studies)	
Leukaemia		Hamster (1 study)	
Harderian tumours	Mice (1 study)		

* RAC notes that haemangiosarcomas are synonymous with angiosarcomas.

RAC agrees with the DS that the absence of human data cannot be considered to be lack of evidence of carcinogenic effects of fluoroethylene in humans. RAC considers that the data for bromoethylene complete the picture regarding the applicability of the read-across between the three structural analogue substances, all of which exhibit similar toxicokinetic and toxicity profiles based on a similar mode of action via CYP2E1 metabolism.

In addition, RAC is of the opinion that the classification of bromoethylene as Carc. 1B (CLP00) is not in contradiction with the proposed classification of fluoroethylene as Carc. 1A. The lack of classification of bromoethylene for Carc 1A is rather considered to be due to the substance not having been reassessed under CLP for classification as Carc. 1A (). Epidemiological data were not available to RAC and could not be identified on fluoroethylene and bromoethylene, likely due to the lack of workers exposure to these substances in the European Union (only 1 Finnish worker exposed to bromoethylene in 2004 (Saalo *et al*, 2006) (IARC, 2008).

RAC conclusion on the proposed read-across and classification of fluoroethylene

In a weight of evidence approach, in reaching its conclusion for classification of fluoroethylene, RAC considers the following:

1) There are no data from humans for fluoroethylene itself but clear evidence of carcinogenicity was shown in animal studies.
2) In epidemiology studies and case studies in humans, the occurrence of liver cirrhosis and liver cancer, particularly hepatic angiosarcomas, and subsequent increased mortality was associated with exposure to chloroethylene. These findings are consistent with the harmonised classification of chloroethylene as Carc. 1A.
3) A read-across approach to fluoroethylene from chloroethylene (for which carcinogenicity to humans as well as animals was shown) and bromoethylene (for which carcinogenicity in animals was shown) is supported by the striking similarities in metabolism, toxicity, mode of action and pattern of carcinogenicity of the three haloethylenes. Therefore, fluoroethylene is expected to have same carcinogenic properties as chloroethylene.
4) The animal data on fluoroethylene indicates that the carcinogenic potency of fluoroethylene is similar (if not higher) compared to chloroethylene.
5) Based on the available data on chloroethylene and considering all the available evidence in a weight of evidence assessment, it can be deduced that, like chloroethylene, fluoroethylene (and bromoethylene, although this is not the subject of this assessment) can elicit tumourigenic effects in humans as well.
6) In the available animal cancer studies with fluoroethylene and chloroethylene, and additional data on the mode of action, are consistent with the observation that this rare tumour type was also induced in human workers exposed to chloroethylene (in the available human data) and thus further support the read-across from chloroethylene to fluoroethylene.
7) Thus, RAC supports the read-across from chloroethylene to fluoroethylene as proposed by the DS.

The lack of human data for fluoroethylene is considered to be the result of a lack of workers having been exposed to the substance.

Regarding classification for carcinogenicity using a read-across approach, RAC notes Section 3.6.2.2.7. of Annex I Regulation (EC) No. 1272/2008. The CLP Guidance further states that the "*specific category depends on the category of the known carcinogen and the degree of confidence in the robustness of the read-across prediction. The category will not be higher than the chemical used to read across from, but normally may be the same. However, a lower category may be applied if the read-across highlights a possible carcinogenic hazard, and thus supports a classification, but there is uncertainty as to the robustness of the read-across prediction or there is evidence, for instance from mechanistic or other studies, that the chemical may be of lower concern for carcinogenicity*".

In the present case where no human data are available for fluoroethylene, taking into account the source substance chloroethylene for which human evidence is available is warranted. Depending on the strength of evidence for the read-across, the same category (Cat. 1A) is to be proposed or if uncertainties exist as to the robustness of the read-across, a lower category may be appropriate (e.g. Cat. 1B).

Taking into account the robust read-across from the data from humans for the human carcinogen chloroethylene (Cat. 1A) as well as the consistent findings in animal carcinogenicity studies on

fluoroethylene and choloroethylene (and the third structural analogue bromoethylene), RAC concludes that **classification of fluoroethylene as Carc. 1A, H350, is warranted**.

GCL/SCL considerations

The DS did not propose a SCL and no SCL has been set for chloroethylene. Since animal cancer data indicated a potentially higher carcinogenic potency for fluoroethylene in comparison to chloroethylene, the need for an SCL is addressed below, but an SCL may not be appropriate due to the read-across approach from chloroethylene and the lack of human data for the substance itself.

In principle, animal cancer studies may also be taken into consideration for setting a SCL. Since fluoroethylene is a gas, route to route extrapolation would be needed to calculate the T25 values, which generates rather large uncertainties and questions whether the T25 derivation according to EC (1999) and Dybing *et al* (1997) referenced in the CLP Guidance is applicable. If T25 calculations were performed for fluoroethylene based on animal data (most sensitive points of departure: adenocarcinoma in mammary glands of female mice at 25 ppm after 9-18 months of exposure, haemangiosarcoma in liver of female rats at 25 ppm after 19-24 months of exposure), their values are between 1 and 100 mg/kg bw/d and would correspond to a medium potency level for which a GCL is appropriate. Thus, RAC recommends the GCL of 0.1 % to be used according to Table 3.6.2 of Annex I to the CLP Regulation and that this be revisited, when a revised guidance on the applicability of the T25 concept for gases is available.

Note D

In addition, 'Note D' should be added to the entry of the substance in in Annex VI, Part 3, Table 3 of CLP, as it has been assigned to chloroethylene as well (Index No 602-023-00-7).

'Note D' states: "Certain substances which tend to polymerise or decompose spontaneously are usually placed on the market in a stabilised form. This is also the form in which they are listed in Part 3 of Annex VI to Regulation (EC) No 1272/2008. However, occasionally these substances are also placed on the market in a non-stabilised form. In this case, the supplier placing such a substance on the market must indicate on the label the name of the substance followed by the words 'non-stabilised'."

In the consultation a comment was received indicating that 'Note D' is to be assigned to fluoroethylenes as well, due to the structural similarity of fluoroethylene and chloroethylene, based on which it can be assumed that fluoroethylenes are also capable of spontaneous polymerisation or decomposition. The commenter further states that in the database "ChemInfo (www.gsbl.de)" it is reported that fluoroethylene is usually transported in a stabilised state, indicating that transport with unstabilised fluoroethylene therefore cannot be excluded. Accordingly, the IARC (1993 and 1995) states that the substance is commercially available at a purity of 99.9% with 0.1% d-limonene being added as a stabiliser, which may indicate that the substance can also exist in an unstabilised form. The IARC further states that fluoroethylene has mainly been used in the production of polyvinylfluoride (PVF) and other fluoropolymers (IARC, 2008) and thus may very well be capable of spontaneous polymerisation.

Therefore, RAC agrees with the proposal to **add 'Note D'** to the entry of fluoroethylene in Annex VI, Part 3, Table 3 of CLP.

Additional references

Additional references included as footnotes.

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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).