CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2

International Chemical Identification:

fluoroethylene

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

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

Index Number: **NA**

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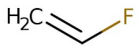
CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	fluoroethylene
Other names (usual name, trade name, abbreviation)	vinyl fluoride fluoroethene
ISO common name (if available and appropriate)	/
EC number (if available and appropriate)	200-832-6
EC name (if available and appropriate)	fluoroethylene
CAS number (if available)	75-02-5
Other identity code (if available)	/
Molecular formula	C2H3F
Structural formula	
SMILES notation (if available)	FC=C
Molecular weight or molecular weight range	46.0436 $g.mol^{-1}$
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	/
Description of the manufacturing process and identity of the source (for UVCB substances only)	/
Degree of purity (%) (if relevant for the entry in Annex VI)	Mono-constitutent substance (gas)

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**
fluoroethylene EC N° 200-832-6 CAS N° 75-02-5	Not applicable (gas)	None	Flam. Gas. 1 – H220 Press. Gas (Liq) – H280 Muta. 2 – H341 Carc. 1B – H350 STOT RE 2 – H373 (liver)

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 3:

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	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			
Resulting Annex VI entry if agreed by RAC and COM	tbd	fluoroethylene	200-832-6	75-02-5	Muta. 2 Carc. 1A	H341 H350	GHS08 Dgr	H341 H350			

Table 4: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)	hazard class not assessed in this dossier To be noted: All industrials notified a self classification Flam. Gas 1 - H220	No
Oxidising gases	hazard class not assessed in this dossier	No
Gases under pressure	hazard class not assessed in this dossier	No
Flammable liquids	hazard class not assessed in this dossier	No
Flammable solids	hazard class not assessed in this dossier	No
Self-reactive substances	hazard class not assessed in this dossier	No
Pyrophoric liquids	hazard class not assessed in this dossier	No
Pyrophoric solids	hazard class not assessed in this dossier	No
Self-heating substances	hazard class not assessed in this dossier	No
Substances which in contact with water emit flammable gases	hazard class not assessed in this dossier	No
Oxidising liquids	hazard class not assessed in this dossier	No
Oxidising solids	hazard class not assessed in this dossier	No
Organic peroxides	hazard class not assessed in this dossier	No
Corrosive to metals	hazard class not assessed in this dossier	No
Acute toxicity via oral route	hazard class not assessed in this dossier	No
Acute toxicity via dermal route	hazard class not assessed in this dossier	No
Acute toxicity via inhalation route	hazard class not assessed in this dossier	No
Skin corrosion/irritation	hazard class not assessed in this dossier	No
Serious eye damage/eye irritation	hazard class not assessed in this dossier	No
Respiratory sensitisation	hazard class not assessed in this dossier	No
Skin sensitisation	hazard class not assessed in this dossier	No
Germ cell mutagenicity	Harmonized classification proposed: Muta 2 – H341	Yes
Carcinogenicity	Harmonized classification proposed: Carc. 1A – H350	Yes
Reproductive toxicity	hazard class not assessed in this dossier	No
Specific target organ toxicity-single exposure	hazard class not assessed in this dossier	No
Specific target organ toxicity-repeated exposure	hazard class not assessed in this dossier	No
Aspiration hazard	hazard class not assessed in this dossier	No
Hazardous to the aquatic environment	hazard class not assessed in this dossier	No
Hazardous to the ozone layer	hazard class not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

There is no current harmonised classification for fluoroethylene.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

There is no requirement for justification that action is needed at Community level: classification proposed for mutagenicity and carcigenicity hazards.

5 IDENTIFIED USES

According to ECHA website, the substance is registered under the REACH Regulation and is manufactured in and / or imported to the European Economic Area, but the tonnage data is confidential. There is no further information on identified uses.

According to IARC monography, vinyl fluoride (fluoroethylene) has mainly been used in the production of polyvinylfluoride (PVF) and other fluoropolymers (IARC, 2008).

6 DATA SOURCES

Data searches encompassed various databases such as PubMed, ToxNet, Scopus, ScienceDirect, Wiley Online Library and Web of Science (3 march 2021). The CLH report also included studies summarized in the monograph by IARC (1995 and 2008) and in the NTP report on carcinogens (2000).
All the REACH registration studies summaries related to genotoxicity and carcinogenicity available on dissemination website have been assessed in this CLH dossier.

7 PHYSICOCHEMICAL PROPERTIES

Table 5: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	gaseous	CRC Handbook of Chemistry and Physics - 87th ed. (internet version 2009)	Experimental study
Melting/freezing point	-160.5°C	IARC (2008)	The literature/ measured melting/freezing point is -160.5°C (IARC, 2008)
Boiling point	-72°C	Cited in Pubchem	In the literature, value for the boiling point is -72.0°C (USCG 1999, EPA DSSTox, OSHA).
Relative density	0.00188 g/cm^3 at 1 atm and 25°C	ECHA site	An estimation based on calculation was made from molecular weight and the Ideal Gas Laws, ρ = m/V. At 1 atm and 25ºC (298.15 K), 1 mol of test substance has the volume of 24.45 L and the molecular weight is 46.02. Therefore, ρ = 46.02/24.45 = 1.88 g/L = 0.00188 g/cm^3.
Vapour pressure	1710000 Pa at 25°C	ECHA site	The vapour pressure is estimated as 1.71E6 Pa calculated at 25°C with MPBPWIN v. 1.43.
Surface tension	/	ECHA site	In accordance with Column 2 adaptation statement of REACH Annex VII, information section requirement 7.6 this study does not need to be conducted since, based on structure, surface activity is not expected and no surface-active properties would be predicted for this compound. Surface activity is not a desired property of the material.

Property	Value	Reference	Comment (e.g. measured or estimated)
Water solubility	9400 mg/L at 80°C and 3.4 mPa	ECHA site	Water solubility of gases is typically measured in a closed system, under pressure, to achieve saturation in water. A value of 9400 mg/L was measured at elevated temperature (80°C) and pressure 3.4 mPa. This value represents a worst case, highest water solubility value for the substance. Under environmental conditions at lower temperature and pressure, the water solubility is expected to be lower. In addition, in open systems, the solubility of this gaseous substance is also significantly lower due to its volatility (vapour pressure = 1.71E6 Pa at 25°C).
Partition coefficient n-octanol/water	0.8975 at 25°C	ECHA site	The octanol/water partition coefficient (log Kow) is estimated at 0.8975 derived using the OECD Toolbox
Flash point	/	ECHA site	In accordance with Section 2 of REACH Annex XI, information requirement section 7.9, this study does not need to be conducted based on the physical state of the molecule. According to ECHA guidance, flash point is only relevant to liquids and low melting solids.
Flammability	Extremely flammable	ECHA site	Experimental study The test substance is extremely flammable. The lower flammability limit is 2.6 % volume in air. The upper flammability limit is 21.7 % volume in air. All industrials notified a self classification Flam. Gas 1 - H220.
Explosive properties	Non-explosive	ECHA site	In accordance with Column 2 adaptation statement of REACH Annex VII, information requirement section 7.11, explosivity testing does not need to be conducted based on a structural assessment of the substance. Examination of the structure indicates that there are no groups associated with explosive properties.
Self-ignition temperature	Hot flame Auto-Ignition Temperature (AIT) = 370°C	ECHA site	The hot flame Auto Ignition Temperature (AIT) of the test substance is 370°C, as determined by EC Testing Method A15.
Oxidising properties	Non-oxidising	ECHA site	In accordance with Column 2 adaptation statement of REACH Annex VII, information requirement section 7.13, measurement of oxidising properties does not need to be conducted based on structural assessment of the substance. The substance contains no oxidising groups and all fluorine atoms are bonded directly to carbon atoms.
Granulometry	/	ECHA site	In accordance with Column 2 adaptation statement of REACH Annex VII, information requirement section 7.14, this study does not need to be conducted for liquids or gases.
Stability in organic solvents and identity of relevant	/	ECHA site	In accordance with REACH Annex XI Section 2, with reference to the guidance mentioned in REACH Art 13 (3) the test guidance “ECHA guidance on information requirements and

Property	Value	Reference	Comment (e.g. measured or estimated)
degradation products			chemical safety assessment Chapter R.7a Endpoint specific guidance" , this study does not need to be conducted since the stability in organic solvents is not considered critical. This would be assessed in individual studies where organic solvents are used.
Dissociation constant	/	ECHA site	In accordance with Section 2 of REACH Annex XI, information requirement section 7.16, this study does not need to be conducted as the test substance has no dissociable groups. According to ECHA Chapter 7 guidance, measurement of pKa is irrelevant as the substance cannot dissociate due to a lack of relevant functional groups.
Viscosity	/	ECHA site	In accordance with Section 2 of REACH Annex XI, information requirement section 7.17, this study does not need to be conducted on solid materials or gases. According to ECHA Chapter 7 guidance, viscosity measurement is only relevant to liquids.

8 EVALUATION OF PHYSICAL HAZARDS

Not assessed in this dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Table 6: Summary table of toxicokinetic studies

Method	Results	Remarks	Reference
In vivo Inhalation 3 Wistar rat males Rats were exposed to the test substance, and also to an analogous test substance, vinyl chloride, in a closed inhalation system (up to 100 ppm). The decline of atmospheric concentration was followed using gas chromatographic analysis. No standard test guideline followed	<u>Metabolism:</u> The calculated concentration of the test substance in tissues of rats exposed to a constant concentration of 100 ppm in air would reach equilibrium very rapidly, within 30 minutes after beginning of exposure. In comparison, the saturation point for the analogous chemical, vinyl chloride, was 250 ppm, thereby demonstrating that vinyl chloride has a significantly greater capacity to produce metabolites. Fluoroethylene is readily absorbed after inhalation. In comparison, calculation of the clearance of vinyl chloride revealed that about 40% of inspired vinyl chloride is absorbed by lung. Pharmacokinetic data indicate that the metabolism of fluoroethylene is saturated at about 75 ppm (~140 mg/m^3) in rats.	Degree of purity ≥ 99 %	Filser & Bolt, 1979
In vivo	<u>Metabolism:</u>	Degree of	Filser &

Method	Results	Remarks	Reference
Inhalation Wistar rat male: number not specified Rats were exposed to the test substance in a closed inhalation system. The decline of atmospheric concentration was followed using gas chromatographic analysis No standard test guideline followed	The equilibrium constant (Keq) was 0.91. The steady state constant (Kst) for the experimental system (V1 = 9.61) was 0.66, and calculated (V1→ ∞) was 0.65. Fluoroethylene is readily absorbed after inhalation. The very low solubility of fluoroethylene in tissues and blood suggests that it rapidly equilibrates within the body during inhalation exposures.	purity ≥ 99 %	Bolt, 1981
In vivo Inhalation 2 Wistar rat males Duration and frequency of exposure: Exposures were extended to 48 to 50 hours and were started by injection of the calculated amount of test substance. Concentrations: Constant exposure to 1250-2000 ppm (concentration was decreasing due to metabolism by the animals but kept within this range by repeated dose injections) Rats were exposed to the test substance in a closed desiccator jar chamber, to concentrations of the test substance at which the metabolizing capacities were saturated (Vmax conditions). Acetone exhalation induced by the test substance's metabolites was measured in this study. The concentrations were measured by gas chromatography. Control experiments (no compound injected) were run in parallel. No standard test guideline followed	<u>Metabolism:</u> In general, the concentrations were kept within the limits by repeated dose injections, and in this range apparent zero-order declines were observed, indicative of a constant metabolic turnover at conditions of saturation (Vmax). The acetone concentration in the system after 48 hours was 133±15 ppm.	Degree of purity ≥ 99 %	Filser, 1982
In vivo Inhalation Sprague-Dawley rat male Exposure regime: 30 minutes Doses/conc.: Three groups of 5 male rats each were exposed to the test substance by inhalation for 30 minutes at a concentration of 3000 ppm. Twenty-four hour urine samples were collected from two of the groups over two weeks. Body weights were measured	<u>Excretion:</u> A significant increase in excretion of urinary fluoride occurred on day 6 post-exposure. There was a significant increase in urine output following exposure. Creatinine excretion was not different from the controls. Potassium excretion was significantly elevated on day 2 and day 6 post-exposure. Sodium excretion was unchanged. Glucose excretion and occult blood in the urine were not affected by exposure. Protein was detected in the urine. Based on body weight there was no difference in growth rates between the exposed and control	Degree of purity: Not reported	Dilley, 1974

Method	Results	Remarks	Reference
every 2-3 days. Fluoride ion concentrations were determined analytically immediately after collection. Glucose, protein, occult blood, and pH were estimated using dipsticks. Sodium and potassium content were determined at the end of the study in samples that had been frozen. The third group of rats was serially sacrificed for pathological examination. No standard test guideline followed	groups. No unusual gross pathologic changes were observed except in the kidney. Marked hyperaemia of the renal medulla was noted and a pale, whitish band in the cortex near the corticomedullary junction. These observations were most pronounced on the third and fourth post-exposure day and nearly absent after 2 weeks. Fluoride appears to be a metabolite of fluoroethylene since it is found in the urine of rats 6 days after exposure.		
In vivo and *in vitro* Inhalation Rat and mouse (*in vivo*); rat CrlCD:BR male, mouse CD-1 male, and human (*in vitro* - microsomes) Exposure regime: 6-8 hours (*in vivo* experiments) 3 hours (*in vitro* partition coefficient experiments) up to 20 minutes (*in vitro* microsomal experiments) Groups of 3 rats or 5 mice were exposed to the test substance in a closed-chamber gas uptake system at starting concentration ranging from 50 to 250 ppm. Partition coefficients were determined and used as parameters for a physiologically based pharmacokinetic (PBPK) model. *In vitro*, microsomes from rat and mouse liver were incubated a sealed vial with the test substance and an NADPH-regenerating system. Headspace concentrations were 10–300 ppm. No standard test guideline followed	Metabolism: *In vivo*, mice showed a higher whole-body metabolic capacity compared to rats (Vmax = 0.3 vs. 0.1 mg/hr-kg in mice vs. rats). The optimized estimated Km was approximately 0.02 mg/L for mice and approximately 0.001 mg/L for rats. Selective inhibition or induction of CYP 2E1 indicated that CYP 2E1 is most likely the only isozyme involved in the oxidation of the test substance in rodents at low airborne concentrations. Inhibition with 4-methylpyrazole completely impaired the test substance uptake in rats and mice, whereas induction with ethanol (rats only) increased the metabolic capacity by two to threefold. *In vitro*, mouse microsomes metabolized the test substance faster than rat microsomes (Vmax was 1.1 nmol/hr-mg protein for rats and 3.5 nmol/hr-mg protein for mice). Km was essentially the same in both species (0.5 μM). *In vitro* in human samples, Vmax for 9 of 10 samples ranged between 0.57 and 1.27 nmol/hr-mg protein and was 3.3 nmol/hr-mg protein for one sample. Km was the same as that found in rodents (0.5 μM). *In vitro*, metabolic rates in human microsomes were found to correlate with the amount of CYP 2E1 as determined by Western blotting and by chlorzoxazone 6-hydroxylation.	Degree of purity > 98 %	Cantoreggi, 1997

9.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

Information related ADME for fluoroethylene:

There is very limited information on absorption, distribution, metabolism and excretion of fluoroethylene.

Absorption:
Fluoroethylene is readily absorbed after inhalation (Filser & Bolt, 1979, 1981; IARC 1995; IARC 2008). Its very low solubility in tissues and blood suggests that it rapidly equilibrates within the body after inhalation exposures.

Distribution:
Fluoroethylene has a low volume of distribution, indeed the blood/air and tissue/air partition coefficients are 0.54–1.82 in rats. Moreover, a fat/blood partition coefficient of 2.4 for this chemical indicates that it is unlikely to be stored to a significant extent in the adipose tissues (Cantoreggi & Keller, 1997).

Metabolism:
The initial oxidation of fluoroethylene results in the formation of fluoroethylene oxide and is probably mediated by cytochrome P450 (CYP) 2E1, as indicated by the inhibition of the metabolism of fluoroethylene by 4-methylpyrazole, whereas induction with ethanol, in rats, increased the metabolic capacity by two to three-fold (Cantoreggi & Keller, 1997). Pharmacokinetic data indicate that the metabolism of fluoroethylene is saturated at about 75 ppm (~140 mg/m^3) in rats (Filser& Bolt, 1979).

Cantoreggi and Keller (1997) demonstrated that microsomes from mice metabolized fluoroethylene more rapidly than those from rats (Vmax = 3.5 and 1.1 nmol/hr per milligram protein, respectively) when exposed *in vitro* to fluoroethylene gas in closed chambers in the presence of an NADPH-regenerating system. Microsomes from human livers were found to metabolize fluoroethylene at a rate similar to that for rat or mouse liver microsomes. Among ten human livers tested, Vmax ranged from 0.57 to 3.3 nmol/hr per milligram protein. Vmax values were directly related to microsomal content of CYP 2E1. Fluoroethylene, similarly to chloroethylene (vinyl chloride), is shown to mediate *in vitro* nicotinamide adenine dinucleotide phosphate dependent inactivation of CYP-450.

Fluoroethylene toxicity 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 epoxide hydrolase) also increased fluoroethylene toxicity (Conolly and Jaeger 1977, cited in Cantoreggi and Keller 1997).

Fluoride appears to be a metabolite of fluoroethylene since it is found in the urine of rats 6 days after exposure. Urinary fluoride concentrations were dose-related at both time periods, but were nonlinear, with a plateau appearing at approximately 2,000 ppm (for both sexes), which suggests saturation of fluoroethylene metabolism (Dilley, 1974).

Available evidence suggests that fluoroethylene is metabolized via the same pathway as that of chloroethylene (**vinyl chloride; VC**; CAS number 75-01-4) and bromoethylene (**vinyl bromide; VB**; CAS number 593-60-2), chemical compounds which have similar chemical structure (NTP, 2000). Pharmacokinetic data imply that the rate of biotransformation of fluoroethylene is about one-fifth that of VC (Bolt *et al.* 1981). Fluoroethylene is metabolized faster than VB, but slower than VC (Bolt *et al*. 1982). VC and VB are metabolized to haloacetaldehydes. Based upon VC metabolism, it is also likely that fluoroacetaldehyde is metabolized to fluoroacetic acid, a potent inhibitor of the Krebs 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. Administration of fluoroethylene has been shown to increase acetone exhalation by rats (Filser *et al.* 1982).

Elimination :
Elevated fluoride excretion was detected in urine. Urinary excretion of fluoride was determined in rats exposed to 0, 200, 2,000 or 20,000 ppm fluoroethylene (0, 376, 3,760, or 37,600 mg/m^{3,} respectively) for six hours/day, five days/week, after 45 and 90 days of exposure. It was noted that urinary fluoride concentrations were consistently higher, after 90 days of exposure to fluoroethylene than after 45 days. Increased excretion of fluoride after 90 days of fluoroethylene exposure may reflect hepatic enzyme induction or saturation of deposition sites (Dilley, 1974).

10 EVALUATION OF HEALTH HAZARDS

10.1 Acute toxicity

Not assessed in this dossier.

10.2 Skin corrosion/irritation

Not assessed in this dossier.

10.3 Serious eye damage/eye irritation

Not assessed in this dossier.

10.4 Respiratory sensitisation

Not assessed in this dossier.

10.5 Skin sensitisation

Not assessed in this dossier.

10.6 Germ cell mutagenicity

Table 7: Summary table of mutagenicity/genotoxicity tests *in vitro*

Method, guideline, deviations if any	**Test substance**	**Relevant information about the study including rationale for dose selection (as applicable)**	**Observations**	**Reference** **Reliability** **(assessed by DS)**
In vitro mammalian chromosome aberration test. According to guideline OECD TG 473 and EPA OTS 798.5375 The study is GLP compliant	fluoroethylene CAS number 75-02-5 Purity 99.99%	Cell type: Chinese hamster Ovary (CHO) Metabolic activation: with and without Duration of exposure: CHO cells were incubated with fluoroethylene at target concentrations of 0, 10%, 40%, 70%, or 100% for five hours without rat S9 metabolic activation or with fluoroethylene at target concentrations of 0, 10%, 25%, 50%, or 75% fluoroethylene for two hours with rat S9 metabolic activation Chromosome aberration assay (without activation): 0, 10, 40, 70, and 100% (target concentrations); 0.0, 8.1, 42.9, 72.3, and 104.1% (analytical concentrations). Chromosome aberration assay (with activation): 0, 10, 25, 50, and 75% (target concentrations); 0.0, 8.3, 25.9, 49.6, and 75.1%	Under nonactivated conditions, cytotoxicity studies showed significant cell cycle delay only at a test substance concentration of 96.3%. With activation, moderate cell cycle delay was observed at 52.1% and severe cell cycle delay was evident at a test substance concentration of ≥ 61.3%. In the chromosome aberration studies, equivocal results were obtained following 5-hour nonactivated treatments (discrepant findings between both independent trials; aberration frequencies within HCD of the laboratory when results combined). After 2-hour treatments with S-9, significant chromosome aberration induction was	Anonymous (1986a) Klimisch score: 2 Key experimental study

		(analytical concentrations). Confirmatory chromosome aberration assay (without activation): 0, 10, 40, 70, and 100% (target concentrations); 0.0, 8.8, 46.5, 77.8, and 111.4% (analytical concentrations) Confirmatory chromosome aberration assay (with activation): 0, 10, 25, 50, and 75% (target concentrations); 0.0, 12.3, 35.4, 63.3, and 91.3% (analytical concentrations) Untreated negative controls: Nitrogen Positive control substance: For trials without activation: 6.44 mM ethylmethane sulfonate (EMS); phosphate buffered saline as the solvent. For trials with activation: approximately 2.5% VC mixed with air. Two independent trials were conducted. The maximum target concentration tested was 100%. At least 100 metaphase cells were evaluated and aberrations per cell, percent abnormal cells, and percent cells with > 1 aberration reported.	seen at test substance concentrations ranging from 8.3-63.3%. Negative and positive control valid. Under the conditions of this assay, the test substance is **positive.**	
Mammalian cell gene mutation assay. Equivalent or similar to guideline OECD Guideline 476 The study is GLP compliant	Fluoroethylene CAS number 75-02-5 Purity 99.99%	Cell type: Chinese hamster Ovary (CHO) Metabolic activation: with and without; Aroclor 1254-induced rat liver S9 Test concentrations: 0, 20, 40, 60, 80, and 100% (nominal) Untreated negative controls: Nitrogen Positive control substance(s): For trials without activation: EMS ; phosphate buffered saline as the solvent. For trials with activation: approximately 2.5% VC mixed with air. Three mutagenicity trials were performed without activation. Data from Trial 1 were not used in the statistical analyses because the actual test concentrations could not be	Preliminary nonactivated cytotoxicity testing indicated a 62% relative survival at 100% test gas; no cytotoxicity was evident in the activated testing. Without activation: No significant increase in the mutant frequency at any of the concentrations tested and no positive dose-response were seen. With activation: The combined statistical analysis of all three trials, based on the nominal test concentrations, showed significant increases in mutant frequencies at all test concentrations. A positive quadratic dose-response was also statistically evident. Negative and positive	Anonymous (1986b) Klimisch score: 2 Key experimental study

		accurately determined. The combined statistical analyses for Trials 2 and 3 were based on the nominal test concentration. Initially, two mutagenicity trials were performed with activation. Although no statistically significant increases in mutant frequencies were demonstrated in either of the two trials with activation when analyzed separately, combined analyses indicated a significant increase at the 60% test level. The large standard deviation between the negative control values in the second trial, however, made the interpretation of these results difficult. Thus, a third trial was performed.	control valid. The test substance was judged **positive** in the CHO-HPRT gene mutation assay when tested **with an activation system.**	
<u>Bacterial reverse mutation assay</u> Equivalent or similar to guideline OECD Guideline 471 GLP compliance: not specified **Deviations** : At least five strains of bacteria should be used: No test on *E. coli. o*r *S. typhimurium* TA102 No detailed results	Fluoroethylene CAS number 75-02-5 Purity 98.68 + area% by G.C. (gas chromatography)	Species: *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 Metabolic activation: with and without; Metabolic activation system: Aroclor 1254-induced rat liver S9 Test concentrations: Trial 1 and 2 (flowmeter values): 0, 5, 10, 20, 40% Trial 3 (flowmeter values): 0, 10, 20, 40, 50% Trial 4 ("corrected" values from chromatographic data): 0, 4.9, 9.6, 15.0, 28.5% Trial 5 ("corrected" values from chromatographic data): 0, 7, 14, 22, 32, 40, 52% Untreated negative controls: filtered air Positive controls: VC	Negative with TA1537, TA 98 and TA100 with and without metabolic activation and TA1535 without metabolic activation. TA1535 with metabolic activation: Statistically significant increases in total revertant colony numbers were observed in trials 2, 3, and 5 ($p \leq 0.01$). All trials were statistically significant at the 0.05 probability level. A significant dose response was observed when combined data from all trials were evaluated. Mutagenic activity in trials 1, 2, 3, 4, and 5 was 1.4, 1.6, 1.9, 1.4, 2.1 times the spontaneous frequency, respectively. Negative and positive control valid. The test substance was **mutagenic for strain TA1535 in the presence of the activation system.**	Anonymous (1979a) Klimisch score: 4
<u>Bacterial reverse mutation assay.</u> Equivalent or similar to guideline OECD Guideline 471 GLP compliance: not	Fluoroethylene CAS number 75-02-5 Purity: Not reported	*S. typhimurium* TA1535, TA1537, TA1538, TA98 and TA100 Metabolic activation: with and without; Metabolic activation system: Aroclor 1254-induced rat liver S9 Test concentrations: 0, 20, 40% Untreated negative controls: filtered	Although there was a slight increase in the reversion rate in strains TA1535 and TA100, this rate exceeded a three-fold increase in the spontaneous background rate in only one case out of 11 trials. Negative and positive control valid.	Anonymous (1976) Klimisch score: 4

specified **Deviations:** No detailed results		air Positive controls: VC	The mutagenicity of the test substance is **unconclusive** in the system.	
Bacterial reverse mutation assay. Equivalent or similar to guideline OECD Guideline 471 GLP compliance: not specified	Fluoroethylene CAS number 75-02-5 Degree of purity 98.68% by G.C.	Species: *S. typhimurium* TA1535, TA1537, TA1538, TA98 and TA100 Metabolic activation: with and without; Metabolic activation system: Aroclor 1254-induced rat liver S9 Test concentrations: 0, 1.0, 5.0, 10.0, 25.0% (trial 1) 0, 1.0, 2.5, 5.0, 10.0, 25.0% (trials 2 and 3) Untreated negative controls: air Positive controls: ethylene oxide	In trial 1, no data was collected for strain TA1538 as there was contamination of the culture on that day. Negative results were obtained in TA1535, TA1537, TA98 and TA100 In trials 2 and 3, there was an increase in revertants only for strain TA100; however it was lower than 2-fold increase and was not dose-related. Negative and positive control valid. The test substance was **not mutagenic in this assay.**	Anonymous (1979b) Klimisch score: 3

Table 8: Summary table of mutagenicity/genotoxicity tests in mammalian somatic or germ cells *in vivo*

Method, guideline, deviations if any	**Test substance,**	**Relevant information about the study (as applicable)**	**Observations**	**Reference** **Reliability** **(assessed by DS)**
Micronucleus assay [chromosome aberration] According to guideline OECD Guideline 474 According to guideline EPA Health Effects Testing Guidelines 50 CFR Part 798, Federal Register Vol 50, No. 188, Sept 27, Subpart 798. The study is GLP compliant	Fluoroethylene CAS number 75-02-5 Purity 99.99% (excluding inhibitor) Inhibitor, D-Limonene 0.31 wt. %	mouse (Crl:CD®-l(ICR)BR) male/female inhalation: gas Duration of treatment: 6 hours, once Post exposure period: 24, 48, or 72 hours Concentrations: 0, 50000, 200000, 400000 ppm (analytical: 0, 50100, 191000, 388000 ppm) by inhalation No. of animals per sex per dose: 15/sex/control, low, and intermediate dose levels; 18/sex/high dose level Positive Control: Cyclophosphamide by ip injection at 20 mg/kg (5 males and 5 females)	No significant depression in the ratio of young, polychromatic erythrocytes to mature, normochromatic erythrocytes was detected in either sex. No statistically significant increases or concentration-related trends in MN-PCEs were seen at the 48 or 72 hour sampling times. At the 24-hour sampling time, females exposed to the intermediate and high dose levels showed statistically significant increases in the frequency of micronucleated polychromatic erythrocytes as compared to their concurrent air controls; a significant concentration-related trend was also present. The 24-hour treated males also showed increased	Anonymous (1987) Klimisch score: 2 Key experimental study

Method, guideline, deviations if any	Test substance,	Relevant information about the study (as applicable)	Observations	Reference Reliability (assessed by DS)
			frequencies of micronucleated polychromatic erythrocytes; however, these were not statistically significant. Negative and positive control valid. On the basis of these findings, the test substance is judged **equivocal in male mice and positive in female mice.**	
Unscheduled DNA synthesis [in vivo mammalian cell study: DNA damage and/ or repair] The test substance was tested for its ability to induce UDS in spermatocytes of male rats. Testicular cells were isolated at 2, 6, and 24 hours after the end of each exposure and cultured in medium containing 3H-thymidine. The study is GLP compliant Only one tested concentration	Fluoroethylene CAS number 75-02-5 Degree of purity 99.99%	Rat (CDF(F-244)CrlBr®), male inhalation (nose-only): gas Duration of treatment: 6 hours/day Frequency of treatment: 1, 2, or 5 consecutive days. Post exposure period: approximately 2, 6, and 24 hours Concentrations: 0, 20000 ppm No. of animals per sex per dose: 15 Control animals: -Negative controls: Conditioned, filtered, house-line air. Phosphate buffered saline (PBS), administered by i.p. injection (2 mL/kg), was the vehicle control for the positive indicator group. -Positive control(s): methyl methanesulfonate in PBS by i.p. injection in a volume of 2 mL/kg at 50 mg/kg	The test substance was not toxic to testicular cells. Following isolation, testicular-cell viability ranged from 91-100% for air-exposed animals and 91-99% for test substance exposed animals. Test substance induced UDS was not observed at any harvest time postexposure following any exposure length. A statistically significant increase in nuclear grains per cell was observed in the positive control (MMS) treated animals compared to vehicle controls. Negative and positive control valid. **Negative**	Anonymous (1990) Klimisch score: 2 Key experimental study
Rodent dominant lethal assay [in vivo mammalian germ cell study: cytogenicity / chromosome aberration] EPA Health Effects Guideline 40 CFR Part 798,	Fluoroethylene CAS number 75-02-5 Purity 99.99%	Rat (CDF(F-244)CrlBr®) male inhalation: gas Duration of treatment: 6 hours/day Frequency of treatment: 5 consecutive days Doses / Concentrations: 0, 200, 2000, 20000 ppm	Test substance exposure had no adverse effects with respect to mortality rate, body weight gain, clinical signs of toxicity, or mating or fertility indices of the adult rats. Pregnancy rates and pre- and post-implantation losses were similar in control and treated dams. The test substance	Anonymous (1988a) Klimisch score: 2 Key experimental study

Method, guideline, deviations if any	Test substance,	Relevant information about the study (as applicable)	Observations	Reference Reliability (assessed by DS)
Subpart 798.5450 and Federal Register, Vol. 40, Part 799.1700. Comparable to OECD TG 478 The study is GLP compliant		(analytical: 195, 2006, 19325 ppm) No. of animals per sex per dose: 40 sexually mature male rats per dose Beginning 2 days after exposure/dosing was completed, each male rat was co-housed with 1 sexually mature, nulliparous, unexposed female. This procedure was repeated weekly, using different females, for 8 consecutive weeks. Females were sacrificed on gestation Day 14. The uterine contents were examined to determine the number of total implantations, resorptions, and live and dead embryos. The ovaries were examined to determine the number of corpora lutea. Preimplantation loss was calculated as the difference between the number of corpora lutea and the number of implantations. Males were sacrificed 10-11 days after the final day of mating. Testes were examined for gross abnormalities, weighed, and preserved in Bouin's fixative. Testes were not examined histologically. Control animals:Yes - Positive control(s): A group of 40 sexually mature male rats was dosed with triethylenemelamine (TEM) in sterile saline on the final exposure day of the other groups. Route of administration: intraperitoneal injection Doses / concentrations: 0.2 mg/kg	exposure did not increase the frequency of dominant-lethal mutations, indicating that the **test substance was not mutagenic to germ cells in the male rat.**	
DNA damage in testicular DNA	Fluoroethylene	Rat Sprague Dawley (F-	Under the test conditions, the test substance did not cause a	Anonymous (1991)

Method, guideline, deviations if any	Test substance,	Relevant information about the study (as applicable)	Observations	Reference Reliability (assessed by DS)
by alkaline elution (Type of genotoxicity: DNA damage and/or repair) The study is GLP compliant. Only one tested concentration.	CAS number 75-02-5 Degree of purity > 99.9%	344/NHSD), male inhalation (nose-only): gas Duration of treatment: 6 hours/day Frequency of treatment: 1, 2, or 5 consecutive days Post exposure period: 2, 6, and 24 hours Concentrations: 0, 20000 ppm No. of animals per sex per dose: 4 animals/ dose/exposure period/post exposure period Control animals: Negative: yes, sham-exposed Positive: methyl methanesulfonate, known to induce DNA single strand breaks, or a positive control, triethylene melamine, known to induce DNA cross links. Testicular cells were harvested 2, 6, and 24 hours after daily exposures of 1, 2, and 5 days to analyze the testicular DNA for DNA single strand breaks and DNA cross links.	significant increase in single strand breaks or cross links in testicular DNA. A statistically significant increase in elution rate was found at one of the 9 time points. However, the difference in rate was very small and not repeated at any other time point in the study. Therefore, it was not considered to be biologically significant. Negative and positive control valid. **Negative**	Klimisch score: 2 Key experimental study
Drosophila SLRL assay (Type of genotoxicity: gene mutation) OECD TG 477 'Genetic Toxicology: Sex-Linked Recessive Lethal Test in Drosophila melanogaster' was deleted on 2nd April 2014. The study is GLP compliant Only one tested concentration.	Fluoroethylene CAS number 75-02-5 Purity 99.8% first sample; used for trials 1 and 2 of the pilot study. 97.9% second sample; used for trial 3 of the pilot study and the actual SLRL assay	Species: Drosophila melanogaster Strain: Oregon-R for exposure, Basc for pair-mating with F1 females Sex: male (200) inhalation: gas Duration of treatment: 24 hours; once Post exposure period: one day before individually mated to sequential groups of females Concentrations: 47.6% test substance with the balance of the mixture being approximately 20% O2 and	Preliminary tests indicated the test substance was neither toxic nor affected the fertility of the treated males compared to the negative control at a concentration of up to approximately 50%. The treated males were mated to virgin Basc females. Over three broods the test substance produced 2.41% lethals compared to 0.08% lethals in the negative control. The positive control was valid with 27.8% lethals. Under the conditions of this test, the test substance was evaluated as being **mutagenic**	Anonymous (1988b) Klimisch score: 3

Method, guideline, deviations if any	Test substance,	Relevant information about the study (as applicable)	Observations	Reference Reliability (assessed by DS)
		30% N2. No. of animals per sex per dose: approximately 200 Negative control: 80% N2 and 20% O2 Positive control: ethyl methanesulfonate	**in the Drosophila melanogaster Sex-Linked Recessive Lethal Test**	

10.6.1 Short summary and overall relevance of the provided information on germ cell mutagenicity

Fluoroethylene is a base-pair substitution mutagen in *Salmonella typhimurium* strain TA1535 with metabolic activation. In addition, it induces hprt forward mutations in CHO cells with rat S9 metabolic activation, and is clastogenic in CHO cells *in vitro*. In a *in vivo* assay for induction of micronucleus formation in bone-marrow, fluoroethylene gave equivocal results in male mice but positive results in female mice. Regarding germ cells, the substance was not mutagenic in a rodent dominant lethal assay in rats and failed to induce single strand breaks or cross-links in testicular DNA in rats. Finally, it induces excessive sex-linked recessive lethal mutations in *Drosophila melanogaster.*

In vitro studies summary:
1) *In vitro* mammalian chromosome aberration test according to OECD TG 473 (Anonymous (1986a)): CHO cells were incubated with fluoroethylene at target concentrations of 0, 10%, 40%, 70%, or 100% for five hours without rat S9 metabolic activation or with fluoroethylene at target concentrations of 0, 10%, 25%, 50%, or 75% for two hours with rat S9 metabolic activation. Statistically significant increases in chromosomal aberrations (CA) occurred at concentration of 10%, 25%, and 50% with metabolic activation. Significant increases in CA were observed only at the highest concentration without S9 metabolic activation (in one of the two trials). A second trial used concentrations of fluoroethylene at 0, 12.3%, 35.4%, 63.3%, or 91.3% with metabolically activated CHO cells. Statistically significant increases in percent cells with more than one aberration were induced at the 35.4% and 63.3% concentrations. Moderate cell cycle delay was observed at 52.1% and severe cell cycle delay was evident at a test substance concentration of ≥ 61.3%. The full study report is not available. This study was performed in 1986 and thus some limitations can be noted when compared to current OECD TG: 100 metaphases per concentration analysed instead of 300 and no clear indication that a continuous treatment was undertaken. Furthermore, the alternative positive control used for trials with activation (approximately 2.5% vinyl chloride mixed with air) was not justified. However, the fact that vinyl chloride was used as a positive control and has a structure similar to fluoroethylene supports the fact that fluoroethylene can also have mutagenic properties. **Overall, the results are considered positive with metabolic activation and equivocal without metabolic activation.**

2) *In vitro* mammalian cell gene mutation assay according to OECD TG 476 (Anonymous (1986b)): fluoroethylene was assessed for induced hprt forward mutations in Chinese hamster ovary (CHO) cells. CHO cells in uncapped tissue culture flasks were exposed to fluoroethylene gas concentrations from 0 to 100% in the ambient environment of glass chambers for five hours (with S9 metabolic activation) or for 18 to 19 hours (without S9 metabolic activation). Cell survival was 62% in a preliminary non-activated cytotoxicity test with undiluted fluoroethylene without metabolic activation; no cytotoxicity was evident in the activated testing. Fluoroethylene was not mutagenic without metabolic activation. However, **in the presence of metabolic activation by S9 liver homogenate from rats, fluoroethylene was mutagenic** at all concentrations (from 20% to 100%), with statistically significant dose-related increases in mutant frequencies, only when the results of the 3 trials were combined.

3) Bacterial reverse mutation assay according to OECD TG 471 (Anonymous (1976 & 1979a); Anonymous (1979b)):
Fluoroethylene was tested for the ability to induce gene mutations in different strains of *Salmonella typhimurium*. Fluoroethylene was tested at exposure concentrations from 0 to 52% with and without exogenous metabolic activation. Fluoroethylene did not induce reverse mutations in strains TA98, TA1537 or TA1538 in the presence of metabolic activation, nor in any strain in the absence of metabolic activation.
Despite the fact that the level of details in the disseminated dossier is very limited, it is reported that fluoroethylene induced a slight but statistically significant increases ($P < 0.01$) in mutation frequency (up to 2.1-fold) in strain TA1535 with metabolic activation (Anonymous 1979a). The test substance was considered mutagenic for strain TA1535 in the presence of the activation system. Moreover, fluoroethylene induced an increase in mutation frequency (>3-fold in only one case out of 11 trials) in TA1535 and TA100 and a slight increase (< 2-fold increase) in strain TA100 with metabolic activation in the others studies (Anonymous 1976 & 1979b, respectively). Overall, **non consistent findings were reported in the Ames assays with fluoroethylene.**

In vivo studies summary:
Somatic cells:
1) Study performed according to OCDE 474 (Anonymous. 1987): Mammalian bone marrow cytogenetic test (metaphase analysis) in mice: fluoroethylene gave equivocal results in males and positive results in females for induction of micronuclei in bone marrow polychromatic erythrocytes (PCEs) of 43-day-old CD-1 mice.
The mice were exposed by inhalation to mean fluoroethylene concentrations of 0, 50 100, 191 000, or 388 000 ppm (0, 94 348, 359 689, or 730 678 mg/m^3) for 6 hours. No statistically significant increases in micronucleated PCEs or concentration-related trends were observed in both sexes at the 48- and 72-hour sampling times. At 24-hour sampling time, the frequency of micronucleated PCEs in female mice showed a significant concentration-related increase at the 191 000 and 388 000 ppm exposure levels, confirmed by scoring of additional PCEs. The males in the low and high exposure groups exhibited increased frequencies of MN-PCEs as compared to the concurrent negative control groups but these increases were not statistically significant ($p=0.09$) possible due to the relatively high number of MN-PCEs in the concurrent 24-hour negative control group. However, when compared to the pooled negative control values across all sacrifice times, the increase was significant ($p=0.004$). No significant depression of the ratio of PCEs to normochromatic erythrocytes (NCE) was seen in the fluoroethylene-exposed mice. Overall, **fluoroethylene induced micronuclei in bone marrow cells of female mice. In males, the results were judged equivocal.** Nevertheless, these results show a lower sensitivity of this test in male mice

Germ cells:
2) *In vivo* mammalian cell study (DNA damage and/ or repair): the test substance did **not induce UDS in rat spermatocytes** following exposure by inhalation (2000 ppm; 6h/day for 1, 2 or 5 consecutive days) (Anonymous, 1990).

3) Study with protocol comparable to OECD TG 478 (Anonymous. 1988a): Groups of 40 male Crl:CD®BR rats were exposed by inhalation to fluoroethylene at concentrations of 0, 200, 2,000, or 20,000 ppm (0, 376, 3760, or 37600 mg/m^3) six hours/day for five days and then mated with unexposed females. Test substance exposure had no adverse effects with respect to mortality rate, body weight gain, clinical signs of toxicity, or mating indices of the adult rats. Fertility was significantly lower for females mated to the 20 000 ppm group compared to control females during mating week 3. However, this was attributed to the relatively high fertility rate observed in the control rats that week. The fertility in the 20 000 ppm group (75%) was within the range of historical control fertility (52-98%) found with this species at the testing laboratory and therefore the lower fertility was not considered a treatment-related effect. Dossier submitter does not have more information on the validity of historical controls data. Pregnancy rates and pre- and post-implantation losses were similar in control and treated dams. The test substance exposure did not increase the frequency of dominant-lethal mutations, indicating that the test substance was **not mutagenic to germ cells in the male rat**.

4) Testicular-cell DNA from groups of male Sprague-Dawley rats tested by nose-only inhalation exposure to fluoroethylene at 0 or (2%) 20,000 ppm (37,600 mg/m^3) for six hours/day for one, two, or five consecutive

days showed no significantly increased frequencies of single strand breaks or cross-links. Fluoroethylene did **not induce unscheduled DNA synthesis in pachytene spermatocytes, nor single strand breaks or cross-links in testicular DNA of male rats** (Anonymous. 1991)**.**

5) According to OECD TG 477 (deleted in 2014) (Anonymous. 1988b): Fluoroethylene caused excessive sex-linked recessive lethal mutations in *Drosophila melanogaster*. Males (N = 198) were exposed to fluoroethylene at air concentrations of 47.6% for 24 hours and then mated with untreated females. The progeny exhibited a significant increase ($P < 0.01$) in the frequency of sex-linked recessive lethal mutations compared with controls. Fluoroethylene exposure resulted in the production of 100 lethal mutations (2.4%) in the F2 progeny, compared with 5 lethal mutations (0.08%) among F2 progeny of flies not exposed to fluoroethylene. Survivability among the fluoroethylene-exposed males was 86.4%. **Fluoroethylene induced sex-linked recessive lethal mutations in *Drosophila melanogaster*** at exposure concentrations of 47.6% for 24 hours.

10.6.2 Comparison with the CLP criteria

Category 1: "Substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans. Substances known to induce heritable mutations in the germ cells of humans."

Category 1A: "The classification in Category 1A is based on positive evidence from human epidemiological studies. Substances to be regarded as if they induce heritable mutations in the germ cells of humans."

Assessment and conclusion:
No human epidemiological studies are available so Cat 1A is not justified.

Category 1B: "The classification in Category 1B is based on:
– positive result(s) from *in vivo* heritable germ cell mutagenicity tests in mammals; or
– positive result(s) from *in vivo* somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. It is possible to derive this supporting evidence from mutagenicity/genotoxicity tests in germ cells *in vivo*, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or
– positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people."

Assessment and conclusion:
Regarding *in vivo* heritable germ cell mutagenicity tests in mammals:

- Fluoroethylene induces excessive sex-linked recessive lethal mutations in *Drosophila melanogaster.* Because the OECD guideline was deleted since 2014, this study is not used for classification purpose.
- Fluoroethylene was negative in *in vivo* germ cells mutagenicity studies in mammals. Fluoroethylene did not increase the frequency of dominant-lethal mutations, indicating that the test substance was not mutagenic to germ cells in the male rat. Moreover, studies related to DNA damage and/or repair were negative in testicular cells of rats.

Regarding *in vivo* somatic cell mutagenicity tests in mammals:

- In a micronucleus assay, treated male mice showed increased frequencies of micronucleated polychromatic erythrocytes at 24h sampling time; however, these were not statistically significant. Fluoroethylene induced micronuclei in bone marrow cells of female mice at exposure concentrations of 19.1% or 38.8% at 24h sampling time. On the basis of these findings, the mutagenicity of the substance was judged equivocal in male mice and positive in female mice.

Regarding ability of the substance or its metabolite(s) to interact with genetic material of germ cells, there are no specific data.

Classification as Muta. Cat 1B is not justified based on these results.

Category 2: "Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans.
The classification in Category 2 is based on:
– Positive evidence obtained from experiments in mammals and/or in some cases from in vitro experiments, obtained from:
– Somatic cell mutagenicity tests *in vivo*, in mammals; or
– Other *in vivo* somatic cell genotoxicity tests which are supported by positive results from in vitro mutagenicity assays".

Assessment and conclusion:
In vivo: the substance was judged equivocal in male mice and positive in female mice in a *in vivo* micronucleus assay. Fluoroethylene induces excessive sex-linked recessive lethal mutations in *Drosophila melanogaster.*
In vitro:

- Fluoroethylene tested at concentration up to 40% is a base-pair substitution mutagen in *Salmonella typhimurium* strain TA1535 with metabolic activation.
- In CHO cells, after a 2-hour treatment with S9, significant chromosome aberration induction was seen at test substance concentrations ranging from 8.3-63.3%. Under the conditions of this assay, the test substance is positive. The test substance exhibited clastogenic activity in CHO cells with S9 activation. Without activation, the findings were equivocal.
- Significant increases in mutant frequencies were evident in the activated testing at nominal atmospheric concentrations ranging from 20% to 100%. The test substance was judged positive in the CHO-hprt gene mutation assay when tested with an activation system.

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.

An overall assessment of *in vitro* and *in vivo* genotoxicity studies on fluoroethylene show that classification as Muta. Category 2 for mutagenicity according to CLP criteria is justified.

Moreover, it was concluded in NTP and IARC reports that fluoroethylene was shown to be mutagenic in bacteria, Chinese hamster ovary cells and *Drosophila* after metabolic activation (NTP, 2000 and IARC, 2008).

10.6.3 Conclusion on classification and labelling for germ cell mutagenicity

Based on the arguments given above, fluoroethylene warrants classification as Muta. Cat 2 (H341).

10.7 Carcinogenicity

Table 9: Summary table of animal studies on carcinogenicity

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference** **Reliability** **(assessed by DS)**
Carcinogenicity: inhalation **Rats/** Crl:CD®BR Sex: male/female	Fluoroethylene > 99.94 % Inhalation: gas / whole body	Because of high mortality, animals exposed to 250 ppm were killed on day 657 and on day 586 for animals exposed to 2500 ppm (about 25% survival). Slight decrease in mean BW gain (6-15%) at 25 and 250 ppm but not at 2500 ppm at final sacrifice.	Anonymous (1992) Bogdanffy *et al.* (1995)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference Reliability (assessed by DS)
95 /sex /group according to US-EPA TSCA guidelines EPA OTS 798.3300 The study is GLP compliant. Historical control data are not available in the full study report.	6 hours/day, 5 days/week (weekends and holidays excluded) up to 2 years. Interim examinations at 12 and 18 months. Concentrations: 0, 25, 250, 2500 ppm	**Non-neoplastic lesions:** At interim and final sacrifice: Increased incidences of foci of hepatocellular alteration (which occurred in all treated male groups and 250 and 2500 ppm female groups) and sinusoidal dilatation in the liver (which occurred in all treated groups). Several other lesions secondary to test substance-induced neoplasms. **Neoplastic lesions:** At the 12-month interim sacrifice, hepatic hemangiosarcoma was noted in 2 female rats of the 2500 ppm group. Zymbal's gland tumours were also observed in 4 male and 4 female rats of the 2500 ppm exposure group. 1 case of hepatocellular carcinoma in males of the 2500 ppm group. At the 18-month and final sacrifices, the total incidences of **hepatic hemangiosarcoma** noted among rats of the 0, 25, 250, and 2500 ppm groups through the final sacrifice were 0/80, 5/80, 30/80, and 20/80, respectively, for males, and 0/80, 8/80, 19/80, and 15/80, respectively, for females. The lower incidence in the 2500 ppm concentration groups relative to that of the 250 ppm groups probably is a result of early mortality. Associated with these tumours were focally extensive areas of necrosis. Metastases were frequently found in the lungs. The incidences of **Zymbal's gland tumours** among rats of the 0, 25, 250, and 2500 ppm groups through the final sacrifice were 0/80, 2/80, 3/80, and 11/80, respectively, in males, and 0/80, 0/80, 1/80, and 12/80, respectively, in females. Since Zymbal's gland was not collected as a target tissue (the tumours observed were collected from gross lesions), and since early mortality was observed among exposed rats, the true incidence of this tumour is likely to be higher. There was an increased incidence of **hepatocellular adenoma and carcinoma** in females. Three carcinomas were noted in females of the 2500 ppm group. All other tumours were adenomas. The combined incidences of hepatic adenoma/carcinoma of the 0, 25, 250, and 2500 ppm females were 0/80, 4/80, 9/80, and 8/80, respectively. **Cell proliferation evaluation:** There were no changes in labelling indices related to test substance exposure.	Klimisch score: 1
Carcinogenicity:	Fluoroethylene	Because of high mortality, animals exposed to 250 ppm	Anonymous

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference Reliability (assessed by DS)
inhalation **Mice** / Crl:CD®-1(ICR)BR Sex: male/female 95 /sex /group according to EPA TSCA guidelines EPA OTS 798.3300 The study is GLP compliant. Historical control data are not available in the full study report.	> 99.94 % Inhalation: gas / whole body 6 hours/day, 5 days/week (weekends and holidays excluded) up to 18 months Interim examinations at 6 months. Concentrations: 0, 25, 250, 2500 ppm	were killed between day 412-459 and between 375-450 for animals exposed to 2500 ppm (about 25% survival). Mean body weight gain of the 2500 ppm male mice was 17% lower than control. **Non-neoplastic lesions:** Non-neoplastic lesions, considered precursors to test substance-induced neoplasms were present: bronchioloalveolar hyperplasia in the lung (2500 ppm), hypertrophy/hyperplasia/angiectasis and basophilic foci (25 and 2500 ppm males) in the liver, mammary gland hyperplasia (all treated females), and acinar hypertrophy/hyperplasia in the Harderian gland. Several other lesions secondary to test substance-induced neoplasms. **Neoplastic lesions:** Bronchioloalveolar adenoma and hepatic hemangiosarcoma were the primary lesions observed at the six month sacrifice. **Bronchioloalveolar adenomas** were increased in all treated groups at the final sacrifice. Multiplicity of adenomas was also increased and had a relatively short latency to tumour onset and thus appeared to be the most sensitive indicator of test substance-induced cancer. Overall incidences of primary lung tumours in male mice of the 0, 25, 250, and 2500 ppm groups were 11/81, 45/80, 52/80, and 56/81, respectively. These incidences in female mice were 9/81, 24/80, 47/80, and 53/81, respectively. **Hepatic hemangiosarcoma** were present in all exposed mice (male mice of the 0, 25, 250, and 2500 ppm groups: 1/81, 16/80, 42/80, and 42/81, respectively; female mice: 0/81, 13/81, 25/80, and 32/81, respectively). One mouse of the 2500 ppm group died on test day 162 of an hepatic hemangiosarcoma. This was the earliest diagnosis of this tumour type in mice. **Extrahepatic hemangiosarcoma and haemangioma** were also observed in the peritoneum, mammary gland, ovaries, and epididymides (25 ppm only). These tumours occurred with reduced frequency and increased latency relative to those in the liver. An increased incidence of **hepatocellular adenomas** was present in 25 ppm males. The tumour incidence was not statistically different from controls (7/67 in the	(1992) Bogdanffi *et al.* (1995) Klimisch score: 1

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference Reliability (assessed by DS)
		control group versus 15/69 in the 25 ppm 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,** primarily adenocarcinomas, were present in all treated females. The overall incidences of mammary gland neoplasms (adenoma, adenocarcinoma and fibroadenoma combined) in female mice of the 0, 25, 250, and 2500 ppm groups were 0/77, 22/76, 20/78, and 22/77, respectively. Increased incidences of **adenomas of the Harderian glands** were present in all treated groups of mice relative to controls. Incidences were greater in male groups (3/66, 13/69, 12/66 and 31/62) compared to females (1/64, 7/61, 6/66 and 12/66). **Cell proliferation evaluation:** Microscopic lesions noted at the 369 day evaluation included bronchioloalveolar hyperplasia and adenomas, hepatocellular hyperplasia at 250 and 2500 ppm, and liver hemangiosarcomas at 2500 ppm. Increases in labeling indices were sporadic. A trend towards increasing hepatocellular proliferation was noted among male mice at day 18. The hepatocyte labelling index was also increased in 2500 ppm males at day 369. Large standard deviations about the mean hepatocyte labelling indices precluded statistical significance.	

Rats 2-year cancer bioassay

Groups of 95 male and 95 female Crl:CD®BR rats were exposed to 0, 25, 250, or 2500 ppm of fluoroethylene for 6 hours per day, 5 days per week, for up to 2 years, weekends and holidays excluded (Anonymous, 1992; Bogdanffi, 1995). Slight decreases in mean body weight gain (6-15%) were noted among rats of the 25 and 250 ppm groups, but not the 2500 ppm group, when evaluated through final sacrifice. There were no unique or unusual incidents of clinical signs that were associated with substance toxicity. Survival was decreased in male rats of the 250 and 2500 ppm groups and female rats of all substance-exposed groups compared to controls leading to sacrifice of the two highest dose groups before the end of the study. Early mortality occurring in the second year of exposure was primarily related to haemorrhage from hepatic hemangiosarcoma. 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-dependent. 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, and fluid of the peritoneal cavity; and masses of the head, face and periaural area; and abscesses of the face. Non-neoplastic lesions, with increased incidences in test substance-treated groups, were foci of hepatocellular alteration (which occurred in all

treated male groups and 250 and 2500 ppm female groups) and sinusoidal dilatation (which occurred in all treated groups). Microscopically, these lesions were correlated with hepatic hemangiosarcoma, hepatocellular adenoma and carcinoma, metastatic lung tumours, and Zymbal's gland tumours (tumor originating from an auditory sebaceous gland that opens into each external ear canal known as Zymbal's gland). The incidences of these lesions were concentration-related in all exposed groups. Hepatic hemangiosarcoma appeared to be the sentinel lesion in rats. The first hepatic hemangiosarcoma appeared on test day 362. Higher incidence of tumours occurred from the lowest tested concentration of 25 ppm. The lower incidence in the 2500 ppm concentration groups relative to that of the 250 ppm groups probably is a result of early mortality.

Tissues from animals in the control and 2500 ppm groups were evaluated for cell proliferation initially. The remaining tissue collected from all animals were processed and evaluated for cell proliferation as needed to determine a NOEL. Based on the results of previous studies, the liver was evaluated for cell proliferation at all exposure concentrations tested. There were no increases in cell proliferation of the organs examined that were consistent and could be related to substance exposure.

Table 10: Neoplastic microscopic observations in target organs of male and female rats necropsied during 0-12 months, 13-18 months and 19-24 months

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				
Hemangiosarcoma	0/12	0/14	0/14	2/18
Zymbal's gland				
Carcinoma, sebaceous/squamous cell	0/12	0/5	0/5	4/18

13-18 months	Concentrations			
Dose (ppm):	0	25	250	2500
Male rats				
Liver				
Hemangiosarcoma	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				
Hemangiosarcoma	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

19-24 months	Concentrations			
Dose (ppm):	0	25	250	2500
Male rats				
Liver				
Hemangiosarcoma	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				
Hemangiosarcoma	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

* Incidences which were statistically significant by Cochran-Armitage trend test and/ or Fisher's exact test ($\alpha < 0.05$)

Table 11: Summary of neoplastic observation in rats

Tumor type	**Tumors incidence/ number examined**			
	Doses (ppm)			
	0	**25**	**250**	**2500**
Rats (Crl:CD®BR) : Males				
Liver				
Hemangiosarcoma	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				
Hemangiosarcoma	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.

Under the conditions of this study, the substance was carcinogenic in male and female rats at concentrations greater than or equal to 25 ppm. A no-observable adverse effect level (NOAEL) was not determined. Based on this information,the LOAEL for carcinogenicity was determined to be 25 ppm (47 mg/m^3).

Mouse 2-year cancer bioassay

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

(Anonymous, 1992; Bogdanffi, 1995). Survival was decreased in male mice of the 250 and 2500 ppm groups and female mice of all test substance-exposed groups compared to controls leading to sacrifice of the two highest dose groups before the end of the study. Early mortality was primarily related to haemorrhage from hepatic hemangiosarcoma and mammary gland neoplasm. Mean body weight gain of the 2500 ppm male mice was 17% lower than control, when evaluated through final sacrifice. 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, considered precursors to test substance-induced neoplasms were present: bronchioloalveolar hyperplasia in the lung, hypertrophy/hyperplasia/angiectasis and basophilic foci (25 ppm males) in the liver, mammary gland hyperplasia, and acinar hypertrophy/hyperplasia in the Harderian gland. Microscopically, these lesions were correlated with bronchioloalveolar adenoma; hepatic hemangiosarcoma; and mammary gland adenocarcinoma. The incidences of these lesions were concentration related in all exposed groups. Bronchioloalveolar adenoma appeared to be the sentinel lesion in mice; the first appeared on test day 89. The first hepatic hemangiosarcoma appeared on test day 162. There were no increases in cell proliferation of the organs examined that were consistent and could be related to test substance exposure. Mild increases were noted in the liver of male mice but large standard deviations precluded meaningful conclusions. The spectrum of test substance-induced tumours is similar to that induced by other similar test substances in mice.

Table 12: Neoplastic microscopic observations in target organs of male and female mice necropsied during 0-6 months and 7-18 months

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				
Hemangiosarcoma	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

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				
Hemangiosarcoma	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
Hemangiosarcoma	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

* Incidences which were statistically significant by Cochran-Armitage trend test and/ or Fisher's exact test ($\alpha < 0.05$)

Table 13: Summary of neoplastic observation in mice

Tumor type	**Tumors incidence/ number examined**			
	Doses (ppm)			
	0	**25**	**250**	**2500**
Mice (Crl:CD®-1(ICR)BR) : males				
Lungs				
Primary lung tumors	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 %)	1/80 (1.25 %)	4/80 (5.0 %)	4/81 (5.0 %)
Liver	1/81 (1.23 %)	16/80 (20 %)	42/80 (52.5 %)	42/81 (51.8 %)
Hemangiosarcoma	7/81 (8.64 %)	15/80 (18.75 %)	5/80 (6.25 %)	3/81 (3.7 %)
Hepatocellular adenoma	2/81 (2.47 %)	2/80 (2.5 %)	1/80 (1.25 %)	0/81
Hepatocellular carcinoma				
Harderian gland adenoma	3/80 (3.75%)	13/79 (16.45%)	12/80 (15%)	31/80 (38.75%)
Mice (Crl:CD®-1(ICR)BR) : females				
Lungs				
Primary lung tumors	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				
Hemangiosarcoma	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	0/79	0/80	0/78	1/79 (1.26 %)

Tumor type	Tumors incidence/ number examined			
	Doses (ppm)			
	0	25	250	2500
Adenoma	0/79	22/80 (27.5 %)	20/78 (25.6 %)	19/79 (24 %)
Adenocarcinoma	0/77	22/76 (28.9%)	20/78 (25.6%)	20/77 (25.97%)
Adenoma, adenocarcinoma, fibroadenoma (combined)	1/81 (1.23%)	7/81 (8.64%)	6/79 (7.59%)	12/81 (14.81%)
Harderian gland adenoma				

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

Under the conditions of this study, the test substance was carcinogenic in male and female mice at concentrations greater than or equal to 25 ppm. No NOAEL was determined in the study. The LOAEL was 25 ppm based on test substance-related tumours in male and female animals at concentrations greater than or equal to 25 ppm, the lowest concentration tested.

Table 14: Summary table of human data on carcinogenicity with closely related substance

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Epidemiological cohort studies of workers exposed to vinyl chloride	Vinyl chloride (VC)	2 large epidemiological multicentric cohort studie in vinyl chloride industry in North America and in Europe. Additional information is provided by several smaller cohort studies.	Sufficient evidence for carcinogenicity to humans. VC causes angiosarcomas of the liver. It has also been associated with brain and lung tumor's.	IARC 2008 TC C&L

There are no human data on carcinogenicity for fluoroethylene, neither with the analoguous substance, vinyl bromide. However, several human data are available for another analoguous substance, vinyl chloride. Data are summarized in the most recent IARC monograph (2008). Based on sufficient evidence for carcinogenicity in humans, this substance is currently classified as Carc. 1A under CLP Regulation (CLP00).

10.7.1 Short summary and overall relevance of the provided information on carcinogenicity

In rats and mice, exposure to fluoroethylene by inhalation caused dose-dependent tumors in several different tissues. **In rats and mice** of **both sexes**, it caused cancer in the blood vessels of the liver (hepatic hemangio-sarcoma).

In rats, fluoroethylene inhalation resulted in increased incidences of benign liver tumors (hepatocellular adenoma) and cancer of the Zymbal gland (carcinoma) in both sexes. There is also incidence of malignant liver tumors (hepatocellular carcinoma) in female rat at the highest dose (2500 ppm).

In mice, fluoroethylene inhalation resulted in increased incidences in dose-dependent manner of bronchioalveolar adenoma in both sexes. There is increased incidence of hepatocellular adenoma at 25 ppm

in male and at 250 ppm in female. It also causes mammary-gland cancer (primarily adenocarcinoma) in the female mice and benign Harderian gland tumors (adenoma) in both sexes.

Carcinogenicity occurred in these two species from the lowest tested concentration of 25 ppm.

Regarding reduced tumour latency, the available data do not allow to conclude on this point. However, it is noted that, in mice study, bronchioloalveolar adenomas had a relatively short latency to tumour onset and thus appeared to be the most sensitive indicator of test substance-induced cancer. Extrahepatic hemangiosarcoma and haemangioma were also observed in the peritoneum, mammary gland, ovaries, and epididymides (25 ppm only, without dose-response relationship). These tumours occurred with reduced frequency and increased latency relative to those in the liver.

Regarding data on ADME: fluoroethylene is likely metabolized in a similar manner than VC, oxidation via cytochrome P450 to fluoroethylene oxide, followed by rearrangement to 2-fluoroacetaldehyde, which is oxidized to fluoroacetic acid. Human, rat, and mouse liver microsomes metabolize fluoroethylene at similar rates (Cantoreggi and Keller 1997). Fluoroethylene toxicity is mediated via epoxide formation and 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 tumors in experimental animals would not operate in humans also.

Regarding the possibility of a confounding effect of excessive toxicity at test dose: Survival was decreased in male rats and mice (250 and 2500 ppm groups) and female rats and mice of all test substance-exposed groups leading to the sacrifice of animals before the end of the study for the 2 highest doses (no numerical value is nevertheless available). However, only slight decreases in mean body weight gain (6-15%) were noted among rats of the 25 and 250 ppm groups, but not the 2500 ppm group, when evaluated through final sacrifice. In mice the mean body weight gain was only decreased in males at 2500 ppm (-17%). In rats, early mortality occurring during the second year of exposure was primarily related to haemorrhage from hepatic hemangiosarcoma and in mice, early mortality was primarily related to haemorrhage from hepatic hemangiosarcoma and also mammary gland neoplasm. So, the high mortality observed may therefore be linked to tumors rather than to an excessive toxicity as test doses.

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).

The NTP report on carcinogens on fluoroethylene classified the substance as *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals (NTP, 2000). IARC concluded in their evaluation that fluoroethylene is probably carcinogenic to humans (Group 2A) based on inadequate evidence in humans and sufficient evidence in animals (IARC, 2008).

Table 15: Compilation of factors to be taken into consideration in the hazard assessment

Species and strain	Tumour type and background incidence	Multi-site responses	Progression of lesions to malignancy	Reduced tumour latency	Responses in single or both sexes	Confounding effect by excessive toxicity?	Route of exposure	MoA and relevance to humans*
Rats Crl:CD ®BR	Liver Hepatic hemangiosarcoma Benign or malignant tumors (hepatocellular	Yes	Yes (already carcinomas)	No information	Both (for hemangiosarcoma, only females for hepatocellular tumours)	No (high mortality occurred at the 2 highest tested doses but increased tumours	inhalation	Relevant for human

Species and strain	Tumour type and background incidence	Multi-site responses	Progression of lesions to malignancy	Reduced tumour latency	Responses in single or both sexes	Confounding effect by excessive toxicity?	Route of exposure	MoA and relevance to humans*
	adenoma or carcinoma)					already observed from the lowest tested dose and the mortality is primarily due to haemorrhage from hepatic hemangiosarcoma)		
	Zymbal gland Increased incidences of cancer (carcinoma)							Not relevant for human
Mice Crl:CD ®-1(ICR) BR	Liver Increased incidences of hepatic hemangiosarcoma and hepatocellular adenoma	Yes	Yes	No information	both	No (high mortality occurred at the 2 highest tested doses but tumours occurred already from the lowest tested dose and the mortality is primarily due to haemorrhage from hepatic hemangiosarcoma and mammary tumours)	inhalation	Relevant for human
	Lungs benign tumors (bronchiolar/alveolar adenoma)		No	Yes	both			Relevant for human
	Harderian-gland tumors (adenoma)		No	No information	both			Not relevant for human
	Mammary-gland cancer (adenocarcinoma)		Yes (carcinoma)	No information	females			Relevant for human
	Extrahepatic hemangiosarcoma and haemangioma in the peritoneum, mammary gland, ovaries, and epididymides		Yes	No information	both	No (only observed at 25 ppm)		Relevant for human

* Metabolism hypothesis and mutagenicity results suggest that the carcinogenicity of the substance, can be at least partially mediated via a genotoxic mode of action.

10.7.2 Comparison with the CLP criteria

Category 1*: Known or presumed human carcinogens*

A substance is classified in Category 1 for carcinogenicity on the basis of epidemiological and/or animal data. A substance may be further distinguished as:

Category 1A*:* Classification in category 1A concerns substances known to have carcinogenic potential for humans and is largely based on human evidence.

There is no epidemiological data available with fluoroethylene. However, epidemiological data exist with the analogous chemical, vinyl chloride, which is currently classified as Carc. 1A under CLP Regulation.

Read-across argumentation:
According to CLP guidance (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.*
In general the chemicals will share a common structural element or functional group (i.e., a toxiphore) that has been shown to be integral to the underlying mechanism of carcinogenicity for chemicals with this toxiphore in well-conducted studies. These toxiphores can be identified through expert judgement or through automated systems such as (Q)SARs. The read-across should also consider the physico-chemical properties of the chemical and data from other toxicity studies to judge the similarity between the chemicals in terms of bioavailability by relevant routes of exposure and toxicokinetics. The toxicity profile from other studies should also be compared (e.g., acute and repeated-dose toxicity and mutagenicity) and should share similarities in nature and severity. Data from shorter-term toxicity studies may be useful, particularly for non-genotoxic carcinogens, to indicate that the chemicals cause the same underlying pathological changes (e.g., hyperplasia), and act via a common mode of action. 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".

In this context, in order to assess the relevance of reading across from other vinyl halides (Table 16) to fluoroethylene, the following elements have been considered:

1) Physicochemical properties and chemical structure

Table 16: Structural similarity among the vinyl halides:

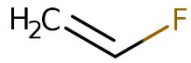
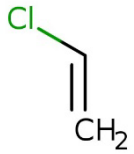
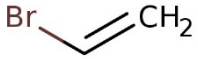
fluoroethylene (vinyl fluoride)	chloroethylene (vinyl chloride)	bromoethylene (vinyl bromide)
CAS 75-02-5	CAS 75-01-4	CAS 593-60-2
		
	Carc. 1A; H350 (CLP regulation)	Carc. 1B; H350 (CLP regulation)

Table 17: Physicochemical properties among the vinyl halides:

	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	0.9106 g/cm³ at 20 °C	1.4933 g/cm³ at 20 °C
Vapour pressure [Pa]	2553390 Pa 19152 mmHg	343970.76 Pa 2580 mm Hg at 25 °C	206800 Pa at 37.8°C 1.033 mm Hg at 25 °C
Partition coefficient	0.8975 at 25°C	1.46	1.57

(log P_{OW})			
Water solubility [g/L] at 20 °C	Slightly soluble 9.4g/L at 80°C and 3.4 mPa	2.7g/L	Insoluble

The strong structural similarity among these three vinyl halides predicts similar biological effects. Indeed, they belong to a class of structurally related chemicals called "simple vinyl halides" and differ only by the halogen substituent (F, Cl or Br). Nevertheless, each halogen produces a similar donor mesomeric effect on the double bond, renders the substance reactive.

Under anhydrous conditions, these compounds react also easily with metals (Cu, Li, Mg) by insertion of metal between the halogen and the carbon.

These halogenated vinyl compounds have widespread industrial use, particularly in the plastics industry, and the primary route of occupational exposure is inhalation.

2) <u>Toxicological profile</u>
Regarding the toxicokinetics data, the similarities between the three vinyl halides are focused on metabolism.

Metabolism
The metabolism of fluoroethylene likely proceeds through the same pathway as the one of the other vinyl halides. However, it is metabolized faster than VB, but slower than VC (Bolt et al. 1982). The metabolic process appears to be saturable, as observed for VC.

The first step in the metabolism pathways for VC is oxidation, which is predominantly mediated by human cytochrome P450 (CYP) 2E1, to form the highly reactive ethylene oxide compound (carcinogenic, mutagenic and reprotoxic), which can spontaneously rearrange to acetaldehyde derivate (Barbin et al., 1975; Holt et al., 2000). Similar pathway via CYP2E1 was demonstrated for fluoroethylene by Cantoreggi & Keller (1997), who reported that an inhibition with 4-methylpyrazole completely impaired the test substance uptake in rats and mice, whereas induction with ethanol (rats only) increased the metabolic capacity by two to threefold. Both metabolites can bind with proteins, DNA and RNA and form etheno-adducts; ethylene oxide compound is the most reactive with nucleotides. They are therefore potentially metabolites responsible for the mutagenesis and carcinogenicity of fluoroethylene and VC.

Fluoroethylene, similarly to VC, is shown to mediate in-vitro nicotinamide adenine dinucleotide phosphate dependent inactivation of CYP (Ortiz de Montellano et al., 1982). Exposure of mice and rats to fluoroethylene results in the formation of N2,3-eG, one of the promutagenic adducts that may be implicated in the mutagenicity and carcinogenicity of the substance (IARC, 2008).

Mutagenicity
There is positive evidence that fluoroethylene is mutagenic. Indeed, fluoroethylene was shown to be mutagenic in bacteria and Chinese hamster ovary cells in particular after metabolic activation. Positive results were also obtained *in vivo* in somatic cells from a micronucleus assay in mice and in *Drosophila melanogaster*. In contrast, the available dominant lethal test is negative. An overall assessment of *in vitro* and *in vivo* genotoxicity studies on fluoroethylene shows that classification Category 2 for mutagenicity according to CLP criteria is justified.

VC and VB are not classified for their mutagenicity properties. However, harmonised classification is rather old (CLP00) and thus it is unknown if an assessment of mutagenic properties with regard to CLP criteria was performed at that time. Information reviewed by the IARC (2008) point to similar mutagenic effects as those reported with fluoroethylene.

The genotoxicity of vinyl chloride has been clearly demonstrated in several *in vitro* systems. Vinyl chloride vapour induced reverse mutation in various strains of *Salmonella typhymurium*. In aqueous or alcoholic solutions, vinyl chloride induced mutations in *Escherichia coli*, *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*. It was also mutagenic in the recessive lethal test in *Drosophila melanogaster,* but not in the dominant lethal test in mice. It induced DNA strand breaks, sister chromatid exchange, micronucleus formation and chromosomal aberrations in rodents. *In vitro*, a higher mutagenic response was obtained in the presence of an exogenous metabolic activation system from rat liver.

VB has been shown to be mutagenic in *Salmonella typhimurium* and in a recessive lethal mutation test with post-meiotic male germ cells of *Drosophila melanogaster*. The comet assay was used to assess the genotoxicity of VB in the stomach, liver, kidney, bladder, lung, brain and bone marrow of male CD-1 mice. The compound (at 2000 mg/kg bw) induced statistically significant DNA damage in all organs except the bone marrow (IARC 2008).

Overall, all three substances are shown to be mutagenic on somatic cells either in *in vitro* and *in vivo* systems. Mutagenic responses are generally higher after metabolic activation suggesting that metabolites are responsible of these effects.

Carcinogenicity

The results from the DK QSAR database are the following:

Carcinogenicity (genotox and nongenotox) alerts by ISS, alerts in:	
- parent compounds	Monohaloalkene (Genotox); Structural alert for genotoxic carcinogenicity
Oncologic Primary Classification, alerts in:	
- parent compound	Halogenated Linear Aliphatic Hydrocarbon Type Compounds

OECD QSAR Toolbox v.4.2 profilers

The alerts from the OECD QSAR toolbox profilers were the same for the 3 vinyl halides, suggesting a potential common mechanistic profile. In addition, epoxides formed during metabolism also lead to additional alerts of concern for carcinogenicity (direct-acting alkylating agent).

For the three vinyl halides, there is a common alert showing similar structural alert for genotoxic carcinogenicity.

Epidemiological data
Epidemiological data is only available for VC. The following information is issued from the assessment by the IARC (2008):

"*Epidemiological evidence for the carcinogenicity of VC in humans derives principally from two large, multicentre cohort studies, one of which was carried out in the USA and the other in Europe. These investigations focused on plants that manufactured vinyl chloride monomer, polyvinyl chloride or polyvinyl chloride products. Additional information is provided by several smaller cohort studies.*
Both of the multicentre cohort studies found a substantial increase in the relative risk for angiosarcoma of the liver, a tumour that is extremely rare in the general population, in exposed workers.

There is no strong epidemiological evidence for associations of exposure to VC 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.

The occurrence of angiosarcoma was strongly associated with exposure to VC but not with exposure to the other chemicals; the risk for brain cancer was highest among workers who had been hired before 1950 but was not associated with exposure to VC."

Based on these results, IARC (2008) concluded that *"there is sufficient evidence in humans for the carcinogenicity of vinyl chloride. Vinyl chloride causes angiosarcomas of the liver and hepatocellular carcinomas."*

Animal data

The carcinogenicity of VC has been studied intensively in various species (rats, mice and hamsters) and routes of administrations. Since only studies by inhalation are available with fluoroethylene and VB, the tumours observed after inhalation exposure to VC are described here. Extrahepatic angiosarcomas related to treatment with VC were observed in three studies in mice and three studies in rats. VC increased the incidence of mammary tumours in mice in six studies, in rats in three studies and in hamsters in one study. Exposure to VC increased the incidence of skin tumours in rats in one study, in mice in one study, and in hamsters in two studies, and increased the incidence of Zymbal gland carcinomas in rats in five studies, with a dose–response pattern in one experiment. VC increased the incidence of lung tumours in mice in six studies, induced tumours of the nasal cavity in rats in one study, increased the incidence of hepatocellular carcinomas in rats in two studies and increased the incidence of glandular stomach tumours in hamsters in one study.

Animal carcinogenicity studies have been conducted in only one species for VB. In a study of inhalation exposure in both sexes of rats, VB caused a significant increase in the incidence of angiosarcomas of the liver, hepatocellular adenomas and carcinomas, and squamous-cell carcinomas of the Zymbal gland.

Regarding fluoroethylene, one study in rats and mice is available. Exposure to fluoroethylene by inhalation caused dose-dependent tumours at several different tissues. In rats and mice of both sexes, it caused cancer of the blood vessels of the liver (hepatic hemangiosarcoma). In rats, fluoroethylene inhalation resulted in increased incidences of benign liver tumours (hepatocellular adenoma) and cancer of the Zymbal gland (carcinoma) in both sexes. There is also an increased incidence of malignant liver tumours (hepatocellular carcinoma) in female. In mice, fluoroethylene inhalation resulted in increased incidences of bronchioalveolar adenoma in a dose-dependent manner in both sexes. There is an increased incidence of hepatocellular adenoma in both sexes. It also causes mammary-gland cancer (primarily adenocarcinoma) in the female mice and benign Harderian gland tumours (adenoma) in both sexes.

Table 18: Summary of cancer types reported in experimental studies after exposure to fluoroethylene, VC or VB by inhalation route.

Cancer type(s)	fluoroethylene (vinyl fluoride)	chloroethylene (vinyl chloride)	bromoethylene (vinyl bromide)
Hepatic angiosarcomas		Mice (3 studies) / Rats (8 studies) / Hamsters (1 study)	Rats (1 study)
Extrahepatic angiosarcomas		Mice (3 studies) / Rats (5 studies)	
Hemangiosarcomas (liver)	Rats (1 study)/ Mice (1 study)	Mice (1 study) / Rats (2 studies)	
Hemangiosarcomas (all sites)	Mice (1 study)	Mice (2 studies) / Rats (2 studies) / Hamster (1 study)	
Hepatocellular carcinomas or adenomas	Rats (1 study)/ Mice (1 study)	Rats (1 study)	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) / Rats (metastases in one study)	
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)		

Ref: Anonymous (1992) ; Bogdanffi *et al.* (1995); IARC (2008). Fluoroethylene IARC mono97-10. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono97-10.pdf

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

Some tumours occurred only after exposure to VC. At first, there are studies on hamsters only with VC, for which there is no possible comparison with the other vinyl halides (VB and fluoroethylene). For example, skin, leukaemia and glandular stomach tumours were observed only in hamsters; there is one rat study with skin epitheliomas (benign tumours at 15 600 or 26 000 mg/m^3 in Sprague-Dawley rats at the same doses in one study out of 3), and one mice study with skin tumours but with low incidence. Secondly, there is also one study out of nine studies, which shows tumours of the nasal cavity in rats after VC inhalation at high dose (13 000 mg/m^3). Finally, concerning extra-hepatic angiosarcomas in rat studies, only few tumours were observed without dose response relationship.

Overall conclusion of carcinogenicity data on humans and animals

- Epidemiological studies of occupational exposure have shown that VC 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 hemangiosarcoma”. All three considered vinyl halides (VC, VB and fluoroethylene) cause this type of tumours in mice and rats. Spectrum of lesions is thus similar among fluoroethylene, VC and VB. Moreover, VC, VB and fluoroethylene cause hepatocellular carcinomas or adenomas and Zymbal gland carcinomas in rats.

- In addition, VC and fluoroethylene cause mammary gland tumours and lung tumours in mice. Finally, IARC concluded that all available studies showed a consistently parallel response between fluoroethylene and VC and they supported that fluoroethylene should be considered to act similarly to the known human carcinogen VC. DS concurs to the same conclusion and thus that fluoroethylene should be considered as VC (Carc 1A; H350) with regards to classification under CLP Regulation.

MoA data

The metabolism of fluoroethylene, VC and VB are thought to be similar. The substances are probably activated by CYP2E1 to (fluoro, chloro, bromo)ethylene oxides, which rearrange to (fluoro, chloro, bromo)acetaldehyde. These metabolites react with nucleic acid bases to form adducts that may be implicated in mutagenicity and carcinogenicity. These include the adduct N7-(2-oxoethyl)guanine.

For VC, these include the major adduct ***N*7-(2-oxoethyl)guanine** (7-OEG), four etheno adducts and 5,6,7,9-tetrahydro-7-hydroxy-9-oxoimidazol[1,2-*a*]purine, as identified *in vitro* and in rats *in vivo*. Increased levels of etheno adducts have also been found in different organs, such as liver, lung and kidney, and in lymphocytes but not in the brain. In rats, adducts have been found equally in non-parenchymal liver cells and in hepatocytes. In humans, **etheno adducts** are formed by lipid peroxidation; there is, however, a paucity of

data on the occurrence of such adducts in vinyl chloride-exposed humans. The mechanism that leads to base misincorporation following adduct formation is still unclear.

For VB, the major adduct is *N*7-(2-oxoethyl)guanosine (Bolt *et al*., 1981). *In vitro* studies have also shown the formation of 1,*N*6-ethenoadenosine.

For fluoroethylene, adducts include *N*7-(2-oxoethyl)guanosine and the cyclic adducts ethenodeoxyguanosine, ethenodeoxyadenosine and ethenodeoxycytidine, which can cause miscoding by modifying base-pairing sites (Bartsch *et al*. 1994, Guengerich 1994). Rats and mice were exposed by whole-body inhalation to 0, 25, 250 or 2500-ppm [0, 47, 470 or 4700 mg/m^3] fluoroethylene for 6 h per day, 5 days per week, for a 2-year period. *N*7-(2-Oxoethyl)guanosine and ethenodeoxyguanosine adducts were found in the liver of rats and mice after 1 year of exposure (Swenberg *et al*., 1999; Holt *et al*., 2000). In addition, a correlation between the amounts of the ethenodeoxyguanosine adducts and the incidence of fluoroethylene-induced angiosarcomas was observed in both species. Similarly to VC, a supralinear response was observed for eG as well as 7-OEG due to saturation of metabolic activation.

Moreover, cell proliferation could be correlated with the tumour response. In a 90-days study, fluoroethylene induced cell proliferation in hepatocytes at 52 000 mg/m^3. In contrast, in the 2-years study, these results were not observed (Bogdanffy *et al*. 1990; Bogdanffy *et al*. 1995). However, the labelling protocol used was not the same, in the cancerogenicity study, the protocol was less sensitive, less likely to detect subtle changes. Hepatic endothelial cells, rather than hepatocytes, appeared to be the primary cellular target of fluoroethylene in liver. Nevertheless, it appeared that the hepatoproliferative activity of fluoroethylene was weak. Thus, the genotoxic activity of fluoroethylene could be the predominant factor contributing to cancer risk. An effect has been suggested through modelling efforts to explain entirely the carcinogenic activity of 2-acetylaminofluorene in mouse liver.

Finally, the spectrum of neoplasms produced by the three vinyl halides 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. Indeed, VC causes angiosarcomas of the liver and hepatocellular carcinomas and VB caused a significant increase in the incidence of angiosarcomas of the liver, hepatocellular adenomas and carcinomas, and squamous-cell carcinomas of the Zymbal gland (IARC 2008).

In conclusion, all these three substances undergo a similar metabolism with the formation of reactive metabolites leading to similar promutagenic adducts leading to carcinogenicity. The evidence of mutagenicity for these compounds was also noted in the genotoxicity studies, where fluoroethylene, VC and VB showed mutagenic properties either in *in vitro* or *in vivo* systems. *In vitro*, a higher mutagenic response was obtained in the presence of an exogenous metabolic activation system.

3) <u>Conclusion</u>

No epidemiological studies of the fluoroethylene carcinogenicity have been identified yet. However, the substance is similar to the known carcinogen VC, which induces liver angiosarcomas and hepatocellular carcinomas in humans (IARC, 2008).

All these three vinyl halides are metabolized to similar DNA-reactive intermediates (haloethylene oxide and haloacetaldehyde) via the cytochrome P450 2E1–dependent pathway and cause genetic damages *in vivo* and *in vitro*. This is confirmed from the available genotoxicity dataset, where positive results were reported in somatic cells for VC, VB and fluoroethylene. Furthermore, the DNA adducts formed are similar for all three vinyl halides, and the etheno adducts can cause DNA miscoding by modifying base-pairing sites (IARC 2008). The fact that VB, VC and fluoroethylene all cause liver hemangiosarcoma in experimental animals and induce the formation of similar DNA adducts support a common mechanism for carcinogenicity.

In conclusion, fluoroethylene should be considered to act similarly to the human carcinogen vinyl chloride (classified as Carc. 1A). In this context, even in the absence of epidemiological data, the level of evidence is

sufficiently robust to consider that fluoroethylene should also be classified as Carc. 1A according to CLP Regulation, based on a read-across from VC.

Based on a read-across from vinyl chloride to fluoroethylene, fluoroethylene warrants a classification as Carc. 1A.

Considering potency in setting specific concentration limits (SCL) for carcinogens:
Since the proposed classification as Carc. 1A is based using a read-across approach with VC, it is not possible to set SCL for fluoroethylene based on its data. Moreover, it has to be noted that harmonized classification for VC is based on epidemiological studies and that there is no SCL for VC currently.

From the animal data available, the mouse seems to be the most sensitive species to carcinogenicity of fluoroethylene. In this species, when considering the liver hemangiosarcoma, the lowest dose of 25 ppm (≈ 16 mg/kg bw/day) is associated with a tumour incidence of 20% in males and the medium dose of 250 ppm with an incidence of 52.5%. This corresponds to a carcinogen of medium potency in experimental animals (1 mg/kg bw/day < T25 value < 100 mg/kg bw/day).

Category 1B *is for substances presumed to have carcinogenic potential for humans. Classification is largely based on animal evidence.*

According to CLP guidance 2017: *"Sufficient evidence of carcinogenicity: a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence. A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites"*

There is sufficient evidence from animal data regarding carcinogenic potential of fluoroethylene. Indeed, exposure to fluoroethylene caused both **benign and malignant** tumors in several different tissues **in two different species: rats and mice**, in two different reliable studies. This fulfils criteria for category 1B.
Even if there is no epidemiological data, fluoroethylene is expected to have the same carcinogenic properties as vinyl chloride based on a weight of evidence approach taken into account structural, toxicokinetics and toxicological considerations. In this context, the absence of human data is not considered as a lack of evidence of carcinogenic effect in humans. The DS judges that a classification as Carc. 1A is more appropriate than Carc. 1B for fluoroethylene.

Category 2 : *Category 2 substances are suspected human carcinogens. Classification is based on evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B.*

Evidence is largely convincing to place the substance in category 1

10.7.3 Conclusion on classification and labelling for carcinogenicity

Based on the arguments given above, fluoroethylene warrants classification as carcinogenic, Cat 1A (H350).

10.8 Reproductive toxicity

Not assessed in this dossier.

10.9 Specific target organ toxicity-single exposure

Not assessed in this dossier.

10.10 Specific target organ toxicity-repeated exposure

Not assessed in this dossier.

10.11 Aspiration hazard

Not assessed in this dossier.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not assessed in this dossier.

12 EVALUATION OF ADDITIONAL HAZARDS

Not assessed in this dossier.

13 ADDITIONAL LABELLING

Not assessed in this dossier.

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15 ANNEXES

Annex I for study summaries

Annex II for confidential information