baua:
Bundesanstalt für Arbeitsschutz und Arbeitsmedizin
Federal Institute for Occupational Safety and Health

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

for

Polyhaloalkene

EC No 468-710-7

CAS RN 754-12-1

Evaluating Member State: Germany

Dated: December 2021

Evaluating Member State Competent Authority

BAuA
Federal Institute for Occupational Safety and Health
Division 5 - Federal Office for Chemicals
Friedrich-Henkel-Weg 1-25
D-44149 Dortmund, Germany

Year of evaluation in CoRAP: 2012

Before concluding the substance evaluation a Commission Implementing Decision in accordance with Article 133(3) to request further information was issued on: 07 September 2015.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State Competent Authority (eMSCA) concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

The Substance, Polyhaloalkene ("R1234yf" or "HFO1234yf"), with EC number 468-710-7, was originally selected for substance evaluation in order to clarify concerns about:

- hazardous degradation products,
- wide-dispersive use,
- high environmental exposure, and
- high tonnage.

During the evaluation additional concerns were identified:

- mutagenicity,
- repeated dose toxicity in rabbits,
- reproductive toxicity,
- potential for endocrine disruption, and
- adequate characterisation of ignition behaviour.

The evaluation of human health exposures and risks was targeted to risks for the general population that may result from the use of polyhaloalkene in mobile air-conditioning of passenger cars.

These risks result from system failures and are expected to be controlled on a vehicle type-specific level according to product safety law and international standards. ISO 13043 and also the international standard SAE (Society of Automotive Engineers) J2773 demand so-called Failure Mode and Effect Analyses (FMEA) or Fault Tree Analyses (FTA) for every passenger car type in which polyhaloalkene is used. Discussing such vehicle type-specific risk analyses is considered to be beyond the scope of a substance evaluation under REACH. Moreover, these studies are typically based on confidential business information from vehicle manufacturers.

Therefore, the main focus of this substance evaluation was placed on providing substance-specific data and discussing the relevance of different exposure conditions and scenarios in order to critically evaluate and potentially improve the input parameters (e.g. the health limit values) used in these risk assessments.

The evaluation considers information in registration updates submitted until 31 August 2018. After this date a direct consumer use has been registered (see confidential annex). This consumer use is not covered by the present substance evaluation. Consumer exposure resulting from use of polyhaloalkene in air conditioning (AC) systems of other vehicles than passenger cars, e.g. in busses (Valeo, 2018), is not covered either.

2. OVERVIEW OF OTHER PROCESSES/EU LEGISLATION

On 22 March 2011, a dossier evaluation decision was finalised[2] which required the registrants to provide a 90-day repeated dose toxicity study in rabbits, by inhalation (method B.29 of Regulation (EC) No 440/2008 or OECD 413) with modifications, robust study summaries for this as well as several other studies, a Derived No Effect Level (DNEL) for consumers and an exposure assessment including exposure scenarios and exposure estimates with respect to consumer use. An appeal was lodged against this decision before

[2] Decision CCH-D-0000001396-72-03/F of 22 March 2011: https://echa.europa.eu/documents/10162/5ca3c767-8eb7-4c8a-8d94-e35e359fcd8c

ECHA's Board of Appeal (BoA). The contested decision was partly annulled following a decision by the BoA on 29 April 2013 to the extent that it required the appellant to conduct the 90-d repeated dose toxicity study.[3]

A second dossier evaluation decision was finalised on 27 July 2015[4] which required the registrants to submit revised DNELs for workers and a revised exposure assessment for the inhalation route and risk characterisation for workers.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the Substance has led the evaluating Member State to the following conclusions, as summarised in Table 1.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION	
Conclusions	**Tick box**
Need for follow-up regulatory action at EU level	x
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	
Restrictions *Based on the intrinsic properties of TFA, the main degradation product of the substance (persistence and mobility)*	x
Other EU-wide measures *Use of substance specific information from this substance evaluation in the application (and potential revision) of ISO 13043.* *Use of substance-specific information from this substance evaluation in other risk assessments for mobile and stationary applications of polyhaloalkene outside REACH*	x
No need for regulatory follow-up action at EU level	

As a result of this substance evaluation process, the following concerns could be clarified:

Human Health

Based on the test submitted in response to the information request from this substance evaluation procedure, it could be clarified that polyhaloalkene does not require classification/ labelling for mutagenicity or carcinogenicity.

Polyhaloalkene caused malformations in a prenatal developmental toxicity (PNDT) study in rabbits, but as these findings were only observed in litters from individuals showing maternal toxicity, the evaluating member state competent authority (MSCA) considers the available data not sufficient to justify classification/ labelling for developmental toxicity. The eMSCA considers the chronic DNEL derived for consumers as sufficiently protective of this effect.

The available data do not indicate that polyhaloalkene has a potential to act as an endocrine disruptor.

The repeated dose toxicity of polyhaloalkene could be assessed based on a new 28-d test.

[3] Decision of the BoA in case A-005-2011 of 29 April 2013:
http://echa.europa.eu/documents/10162/13575/a_005_2011_boa_decision_en.pdf
[4] Decision CCH-D-2114306301-70-01/F from 27 July 2015:
https://echa.europa.eu/documents/10162/30275d00-1048-4acf-9a12-f0044e9e5575

After receiving information from the registrants on low probabilities of small/medium-sized AC system leaks, the eMSCA withdrew an original information request regarding exposure estimations for vehicle occupants upon the release of polyhaloalkene into the passenger compartment from this kind of leaks.

Environment

The substance itself is not persistent in the environment and shows no signs of ecotoxicity or bioaccumulation based on currently available information which would warrant a classification of the substance for aquatic toxicity or identification of the substance as an SVHC under REACH according to Article 57(d) (PBT) or (e) (vPvB). However, polyhaloalkene nearly exclusively degrades to trifluoroacetic acid (TFA) under environmental conditions.

Available monitoring data on TFA and related modelling of environmental emissions suggest that the use of polyhaloalkene as a refrigerant in Mobile Air Conditioning Systems (MACs) is a major source for TFA in the environment.

Based on available information for TFA, the substance is persistent and mobile in the environment, with a marked potential for Long Range Transport (LRTP). Furthermore, TFA exhibits ecotoxic effects. Therefore, environmental emissions of TFA and its precursors, including polyhaloalkene, should be minimised.

The remaining concerns which could not be fully clarified due to outstanding information requirements (cf. Section 7.2) are as follows:

Flammability risk

Due to the fact that the registrants have used a higher ignition temperature of polyhaloalkene than determined by this substance evaluation, the flammability risk is underestimated when not using the auto ignition temperature of 405 °C (EU Method A. 15). Furthermore, according to the European standard EN 13463-1:2009 "Non-electrical equipment for use in potentially explosive atmospheres – Part 1: Basic method and requirements" the use of the auto-ignition temperature in accordance with EU Method A.15 is the state of the art for a risk assessment.

Hazardous degradation products

Accidental exposure to carbonyl difluoride and accidental bystander exposure to hazardous degradation products may be underestimated sources of health risks for the general population quantitative risk assessments for polyhaloalkene. This may be relevant for vehicle type-specific risk assessments under European product safety law and according to ISO 13043. These problems were not clarified in the SAE Risk Assessments provided by the registrants (Gradient, 2009b; Gradient, 2013) and in the studies by German authorities (KBA, 2013) and the European Commission (JRC, 2014b). In addition, health risks from thermal degradation products of Polyhaloalkene in hybrid and fully electric vehicles were not covered by the above mentioned risk assessments. In detail the following aspects could not be clarified in this substance evaluation: Health risks resulting from accidental exposure to carbonyl difluoride (COF_2) were not clarified because amounts and relative proportions of hydrogen fluoride (HF) and COF_2 released as thermal degradation products of polyhaloalkene were not experimentally determined. According to a dossier by the US National Research Council, created in the context of setting so-called 'Acute Exposure Guideline Levels' (AEGLs) (NRC, 2014), COF_2 appears to be more toxic than HF itself as evidenced by the fact that the AEGL-2 values for HF and for COF_2 differ by a factor of ca. 270 and a mixture of these two breakdown products can be expected to be clearly more toxic than HF alone. Exposure to carbonyl difluoride (COF_2) should be considered with conservative assumptions in those scenarios of risk analyses like FTA/FMEA, where thermal decomposition of polyhaloalkene can be expected.

Health risks resulting from accidental bystander exposure were not clarified because quantitative estimations of exposure to thermal degradation products of polyhaloalkene for bystanders have not become available as proposed in the draft decision (cf. section 7.2). This information would have described the spatial distribution of the degradation products over time for scenarios of refrigerant ignition or its contact with hot surfaces when released

due to an accidental rupture of the MAC system. The eMSCA still sees a need for such information in order to substantiate the assumptions in the SAE risk assessments that vehicle occupants will be able to leave the car safely and that no other person in the vicinity of the vehicle will be affected in case of refrigerant ignition, e.g. after a collision. In case of vehicle fires, the theoretical upper margin of HF (and COF_2) concentrations which can be produced by thermal degradation of a refrigerant charge in a vehicle is high and health-relevant concentrations of thermal degradation products of polyhaloalkene around the car cannot be excluded. The argumentation of the registrants that bystanders would walk away due to the irritant/corrosive properties of HF is only valid if they have the possibility to do so before suffering from adverse effects. As no information was provided that would substantiate this assumption, bystander exposure to thermal degradation products should be conservatively assumed in scenarios where polyhaloalkene is thermally decomposed.

Relevance of exposure scenarios

The eMSCA could not request a revised set of exposure scenarios for the general population (cf. section 7.2). This set would have considered the above factors on a data-based level taking into account the results of the latest studies, the information from the other requests, and the specific situation in hybrid and fully electric vehicles. The revised exposure scenarios would have informed not only this substance evaluation, but also the vehicle type-specific assessments performed by the vehicle manufacturers.

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

4.1.1. Harmonised Classification and Labelling

The Substance Evaluation of polyhaloalkene did not identify endpoints for which harmonised classification/labelling (CLH) is warranted.

4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

The Substance Evaluation of polyhaloalkene did not conclude that polyhaloalkene is a Substance of Very High Concern (SVHC).

4.1.3. Restriction

Human health

The evaluation of human health exposures and risks was targeted to risks for the general population that may result from the use of polyhaloalkene in Mobile Air Conditioning Systems (MACs) in passenger cars. These risks result from system failures and depend on a number of vehicle-specific parameters. They are therefore expected to be controlled on a vehicle type-specific level according to product safety law and international standards.

Environment

While the eMSCA concludes based on available information that the substance itself does not pose a risk to environmental organisms, its main degradation product TFA is persistent and mobile in the environment. Due to the relatively fast and complete degradation to TFA, polyhaloalkene is a main source for environmental emissions of TFA.

Due to its persistency and mobility in the environment, emissions of TFA to the environment should be restricted.

It is currently anticipated that TFA and its precursors would fall under the scope of the broad restriction under REACH of per- and polyfluoroalkyl substances (PFAS) which is currently being prepared by the eMSCA and several other MSCAs.

4.1.4. Other EU-wide regulatory risk management measures

This substance evaluation provides new evaluations of toxicity for polyhaloalkene and for its thermal degradation products HF and COF_2. In addition, it discusses the flammability of polyhaloalkene and accidental bystander exposure in cases of vehicle ignition.

This information differs from toxicity values, auto ignition temperature and exposure scenarios used in the SAE Risk Assessments provided by the registrants (Gradient, 2009b, Gradient, 2013). It also differs from the toxicity values in ISO 13043 and should be used in the future general and (vehicle) type specific FTAs and FMEAs for polyhaloalkene. In order to facilitate this for MAC uses, a revision of ISO 13043 should be considered. In the view of the German CA, implementation of a revised ISO 13043 as a mandatory minimum standard for type approval could ensure the use of information from this substance evaluation in further risk assessments.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

Not applicable.

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Indication of a tentative plan is not a formal commitment by the evaluating Member State. A commitment to prepare a REACH Annex XV dossier (SVHC, restrictions) and/or CLP Annex VI dossier should be made via the Registry of Intentions.

Table 2

Follow-up		
Follow-up action	**Date for intention**	**Actor**
Annex XV dossier for restriction (broad PFAS restriction)	2021	Denmark, Germany, the Netherlands, Norway and Sweden

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

The Substance, Polyhaloalkene ("R1234yf" or "HFO1234yf"), with EC number 468-710-7, was originally selected for substance evaluation in order to clarify concerns about:

- hazardous degradation products,
- wide-dispersive use,
- high environmental exposure, and
- high tonnage.

During the evaluation additional concerns were identified:

- mutagenicity,
- repeated dose toxicity in rabbits,
- reproductive toxicity,
- potential for endocrine disruption, and
- adequate characterisation of ignition behaviour.

The outcome/conclusion of the evaluation of the endpoints of concern are briefly summarised in the table below:

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/Conclusion**
Carcinogenicity	Concern refuted. Polyhaloalkene does not require classification/labelling for carcinogenicity.
Mutagenicity	Concern refuted. Polyhaloalkene does not require classification/labelling for mutagenicity.
Reproductive toxicity	Concern refuted. Polyhaloalkene caused malformations in a PNDT study in rabbits at doses showing maternal toxicity. The available information does not warrant classification/labelling for developmental toxicity. The chronic DNEL derived for consumers is considered as sufficiently protective of this effect.
Endocrine disruption	Concern refuted. Available information does not indicate that polyhaloalkene is a potential endocrine disruptor.
Repeated dose toxicity	Concern refuted. Based on a new 28-day study, the endpoint could be assessed.
Exposure of vehicle passengers	Concern refuted. Based on monitoring and modelled data.
Degradation in the environment	Concern confirmed. TFA is relevant degradation product of polyhaloalkene in the environment. The registered use of polyhaloalkene as refrigerant in MAC is considered a major source for environmental emissions of TFA. Based on the available information on the persistence and mobility of TFA and its predicted emissions from degradation of polyhaloalkene under environmental

	conditions, **there is a concern for the environment requiring further regulatory action.**
Flammability risk	Concern unresolved. A higher auto ignition temperature is used by the registrants compared to the information used by the eMSCA, leading to a potential underestimation of the flammability risk. A corresponding information request for further justification has not been formalised in a decision making process.
Hazardous degradation products	Concern unresolved. Assessment of accidential exposure to hazardous degradation products formed during thermal degradation of polyhaloalkene are not covered by the quantitative risk assessment. These may be relevant for vehicle type-specific risk assessments under EU product safety law and according to ISO 13043. A corresponding information request for further justification has not been formalised in a decision making process.
Health risks for bystanders	Concern unresolved. Quantitative estimations of exposure of bystanders to thermal degradation products of polyhaloalkene are not available. A corresponding request for further information has not been formalised in a decision making process.
Relevance of exposure scenarios	Concern unresolved. No revised exposure scenarios have been provided for the general population. A corresponding request for further information has not been formalised in a decision making process. These exposure scenarios would also inform the vehicle type-specific assessments performed by vehicle manufacturers.

7.2. Procedure

Following the evaluation of polyhaloalkene performed by Germany from March 2012 to March 2013, a draft decision with information requirements was sent to the registrants. The draft decision was commented by the registrants and, following the submission of proposals for amendments by other Member State Competent Authorities, the decision was revised by Germany. Its finalisation was sought at the 34th meeting of the Member State Committee (MSC).

The information requests included in the Draft Decision prepared by Germany and discussed in the MSC concerned

- *in vivo* mutagenicity testing,
- experimental data on the amounts and relative proportion of hydrogen fluoride and carbonyl difluoride released as thermal degradation products of polyhaloalkene,
- quantitative estimations, e.g. by dispersion modelling, of exposure to thermal degradation products of polyhaloalkene for bystanders,
- exposure scenarios and exposure estimations for the general population for thermal degradation products of polyhaloalkene,
- a justification for the use of an autoignition temperature (AIT) of 750 °C, and
- an estimation of environmental emissions of polyhaloalkene.

With the exception of the request for further *in vivo* mutagenicity data, unanimous agreement on the decision was not reached by the MSC and, consequently, the draft decision was referred to the Commission according to Article 51(7).

In February 2014, the REACH Committee had a first discussion of the items of the Draft Decision on which no unanimous agreement could be reached in the MSC.[5]

The Commission took an implementing Decision including the *in vivo* mutagenicity information requirement on 07 September 2015 following the procedure outlined in Article 133.[6] It required the registrants to review all available information on toxicokinetics and any effects observed on germ cells and to carry out either a Transgenic Rodent Somatic and Germ Cell Mutation Assay (TGR, OECD 488) or a Comet Assay (OECD 489) depending on the likelihood of polyhaloalkene causing mutagenicity in mammalian germ cells. The Implementing Decision required this specific information on mutagenicity to be provided until 07 September 2017.

Subsequently, the European Commission has not put polyhaloalkene on the agenda of the REACH Committee again to implement a decision on the remaining information requirements from the eMSCA's draft decision. In the meantime, the European Commission has notified Germany of their decision not to reopen the discussion on polyhaloalkene in the REACH Committee.

As no Implementing Decision has been issued by the Commission regarding the remaining information requirements outlined above, not all concerns evaluated by Germany could be clarified within the 12 month examination period for new information provided by REACH according to Article 46(3) which formally expired on 7 September 2018.

The purpose of Substance Evaluation (SEv) is to clarify concerns regarding possible risks a substance may pose to human health and the environment. Furthermore it is the REACH process which allows Member States to request additional information when this is required to clarify such concerns. Since in the present case, as explained above, the European Commission has decided that the registrants will not be required to submit the information, the eMSCA formally concludes the SEv at this point in time, in spite of remaining concerns. To this end, a thorough review has been carried out which included the original evaluation as well as any new relevant information received by the eMSCA since the time the first Draft Decision for the MSC was prepared.

Consequently, due to the reasons outlined above, this evaluation report takes into account registration updates submitted until 31 August 2018.

7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	Polyhaloalkene
EC number:	468-710-7
CAS number:	754-12-1

[5] After the finalisation of the draft decision by the eMSCA, two studies were published which denied a serious risk in the sense of the General Product Safety Directive (Directive 2001/95/EC) and the Framework Directive (Directive 2007/46/EC) from use of polyhaloalkene in vehicles (JRC, 2014b; KBA, 2013). These risk evaluations relied on experiments and considerations regarding the probability of certain collision scenarios with subsequent ignition. In contrast, the present substance evaluation did not aim to discuss details of vehicle constructions and the probabilities of their failure, but to clarify the substance-specific determinants of exposure and risk, i.e. the nature of potentially relevant substances and their toxicity as well as levels of exposure of potentially exposed individuals to be considered in future vehicle(type-)specific risk assessments. Due to this difference in scope, the remaining concerns addressed in the Draft Decision by the eMSCA could not be clarified by the studies by (KBA, 2013) and (JRC, 2014b).

[6] Commission Implementing Decision of 7.9.2015 on the evaluation of the substance polyhaloalkene: https://echa.europa.eu/documents/10162/e23a2e0e-d456-48f0-9d24-2fb4bbf49dca; annex to the Implementing Decision: https://echa.europa.eu/documents/10162/94fc6349-07e7-4072-9ba1-5164b3646393

Index number in Annex VI of the CLP Regulation:	N/A
Molecular formula:	$C_3H_2F_4$
Molecular weight range:	113.99 g/mol
Synonyms:	R-1234yf HFO-1234yf2,3,3,3-tetrafluoroprop-1-ene Opteon™ YF Opteon™ YF Aftermarket

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:

Further information regarding the composition of the substance is contained in a confidential annex to this report.

7.4. Physico-chemical properties

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20 °C and 101.3 kPa	Gaseous
Melting/Freezing point	The substance is completely gaseous at room temperature and can be expected to have an extremely low melting point which is impractical to determine.
Boiling point	29 C at 760 mm Hg
Vapour pressure	580 kPa at 20 C
Surface tension	Surface activity is not expected based on the chemical structure.
Water solubility	198.2 mg/L at 24 °C and pH 7
Partition coefficient n-octanol/water (log K_{ow})	2.0 at 25 C
Flash point	Not applicable (The test item is a gas.)
Flammability	Extremely flammable gas (ASTM E681) Based on the chemical structure and experience in handling and use, pyrophoricity and flammability in contact with water are not expected.
Explosive properties	Not explosive (Based on the theoretical assessment of the chemical structure.)
Oxidising properties	Not oxidising (Based on the theoretical assessment of the chemical structure.)

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Granulometry	In accordance with the column 2 adaptation statement of REACH Annex VII, this study does not need to be conducted for liquids or gases.
Stability in organic solvents	The stability of the test item is not in organic solvents is not expected to be critical.
Dissociation constant	The information requirement is waived by the registrant.
Viscosity	Study scientifically unjustified. Substance is a gas under ambient conditions.
Auto flammability	ca. 405 °C at ca. 102 kPa (EU Method A.15)
Thermal stability	Decomposition products from accelerated aging tests indicated that decomposition is insignificant in the intended use of the test substance as a heat transfer fluid or for use as a refrigerant in the presence of compressor lubrication oils.

7.5. Manufacture and uses

7.5.1. Quantities

Table 6

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☒ 1000- 10000 t	☐ 10000-50000 t
☐ 50000 – 100000 t	☐ 100000 – 500000 t	☐ 500000 – 1000000 t	☐ > 1000000 t	☐ Confidential

7.5.2. Overview of uses

Polyhaloalkene is used as a refrigerant in mobile air conditioning, stationary air conditioning and in refrigeration. A variety of refrigerant blends which contain polyhaloalkene can be found in the international standards on designation and safety classification of refrigerants ISO 817 and ANSI/ ASHRAE Standard 34.

Table 7 summarises the disseminated uses for polyhaloalkene according to the ECHA database.[7]

[7] ECHA Dissemination database on "polyhaloalkene", accessed on 28 August 2019, https://echa.europa.eu/de/registration-dossier/-/registered-dossier/16012/3/1/7

Table 7

USES	
Manufacture	All registrants have indicated that the substance is not produced inside the European Union and therefore manufacture is not relevant for this evaluation. To the eMSCA's knowledge, this information is conclusive and therefore currently no additional information on the manufacturing process and related process conditions are considered necessary.
Formulation	Formulation of preparations for refrigerants, coolants
Uses at industrial sites	Industrial use of functional fluids: Heat transfer fluids – refrigerants, coolants
Uses by professional workers	Widespread indoor and outdoor use of functional fluids (heat transfer fluids – refrigerants, coolants)
Consumer Uses	Indoor and outdoor use functional fluids (heat transfer fluids – refrigerants, coolants)
Article service life	Functional fluid in vehicles, machinery, mechanical appliances, electrical/electronic articles

Polyhaloalkene in polymers

Besides the use as a coolant as described above, the disseminated information on the registration makes a brief reference to polyhaloalkene in polymers: "*For uses as polymers, there are no identified uses since polymerization is taking place out of the EU and the lifecycle of the substance is already over when the polymer is imported to the EU*."

Uses advised against

The following uses of polyhaloalkene are advised against according to the disseminated information from one or more registrations: the use of the substance by consumers in the filling of MACs, direct use of the substance by consumers, use by consumers and professionals in direct and open evaporation applications.

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

Currently, there is no harmonised classification for polyhaloalkene.

The thermal degradation product of polyhaloalkene, hydrogen fluoride (CAS 7664-39-3 EC 231-634-8, Index no. 009-002-00-6) has been included in Annex VI of Reg. (EC) 1272/2008 with the following classification:

Acute Tox 1/H310; Acute Tox 2*/H300, H330; Skin Corr. 1A/H314

For the second known thermal degradation product of polyhaloalkene, carbonyl difluoride (CAS 353-50-4; EC 206-534-2), no harmonised classification and labelling is available.

7.6.2. Self-classification

- In the registration dossier(s)*:*

  Flam. Gas 1 H220 H280

  Specific concentration limit: Flam. Gas 1: 6.2% < C < 12.3%

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory*:*

  Press. Gas (Liq.) H280

- Available self-classifications for hydrogen fluoride do not contain any human health hazard classes beyond those already laid down in the harmonised classification.
- Self-classifications for the second thermal degradation product of polyhaloalkene, carbonyl difluoride (CAS RN 353-50-4; EC number 206-534-2) include the following hazard classes (in different combinations as per notifier): Acute Tox 1/H330, Acute Tox 2/H330, Acute Tox 3/H331, Skin Irrit 2/H315, Skin Corr 1A/H314, STOT SE 1/H370.

The eMSCA notes that the classification criteria for the hazard class "flammable gasses" will be adapted to UN GHS in the wake of the 12th amendment to technical process (ATP) of the CLP regulation. The 12th ATP have entered into force in April 2019 and the changes apply from 17 October 2020.

For polyhaloalkene, self-classification with regard to this hazard class would have to be adapted to the following based on the available information:

Flam. Gas 1B, H221: Flammable gas.

7.7. Environmental fate properties

7.7.1. Degradation

7.8.1.1 Abiotic degradation

Hydrolysis

The registrant states that hydrolysis will be negligible because alkanes and alkenes are types of functional groups that are generally resistant to hydrolysis. Using the QSAR programme HYDROWIN, the half lives of alkenes cannot be estimated properly. Therefore a surrogate analogue (CF3-CHF-CH3) was used for calculation. The surrogate's half life was estimated by the registrant to be in a range of 10^6 to 10^7 which leads to the read-across conclusion that polyhaloalkene is stable to hydrolytic degradation, too.

The hydrolysis study was evaluated already in 2007 by the BE CA in the framework of NONS notification and amended in 2008. The Belgian CA agreed with registrants' (notifiers) discussed results and conclusion.

The eMSCA considers the assessment provided by the registrant as conclusive.

Phototransformation in air

In the registration, a study is provided describing the stepwise atmospheric degradation process from polyhaloalkene to TFA. It is also stated that the first degradation product CF3C(O)F (trifluoroacetylfluoride) is removed from the atmosphere via hydrolysis in about 10 d. However, the submitted information does not contain any information on atmospheric half life of polyhaloalkene being subject of OH-initiated oxidation or degradation by ozone radicals.

Additional information on the environmental fate and behaviour in the registration is provided in the form of study results on atmospheric degradation conducted in a smog chamber. Fourier transformation infrared (FTIR) spectroscopic techniques were used to determine the half lives of polyhaloalkene in reaction with different atmospheric constituents. The rate constants were identified for the reaction with chlorine radicals, hydroxyl radicals and ozone radicals. The registrant came to the conclusion that polyhaloalkene has an atmospheric lifetime of about 11 d. As it is not clear if this value represents the result of all three photolytic degradation pathways named above, additional

information should be included in the registration on whether this constitutes a worst or best case estimation.

As this study represents a more detailed assessment of the photolytic degradation of polyhaloalkene the information reported in the registration should refer to the different degradation pathways and every corresponding estimated atmospheric half life.

Indirect photochemical degradation in the troposphere is considered to be slow based on an estimated OH radical reaction rates (please see Table below), which corresponds to an atmospheric half-life of 14.32 - 14.58 d for the reaction with OH-radicals (24 h d^{-1}; OH radical concentration of $5 \cdot 10^5$ OH cm^{-3}). Comparing this half life with the criterion for long range transport potential (LRTP)[8] of more than 2 d, a potential for LRT can be expected for polyhaloalkene.

Table 8

Available OH reaction rate constants k(OH+$CF_3CF=CH_2$) of polyhaloalkene and therewith calculated half life in air ($T_{1/2\ air}$)		
k(OH+$CF_3CF=CH_2$) [$cm^3\ mol^{-1}\ s^{-1}$]	**$T_{1/2\ air}$ [h]***	**Reference**
$1.1 \cdot 10^{-12}$	350	(Klöpffer and Wagner, 2007)
$1.12\ (+/-\ 0.09) \cdot 10^{-12}$	343.75 (min: 318, max: 374)	(Papadimitriou et al., 2008)
$1.109\ (+/-\ 0.007) \cdot 10^{-12}$	347.16	(Orkin et al., 2010)

* $T_{1/2\ air} = \ln 2 \cdot (5 \cdot 10^5\ OH\ radicals \cdot cm^{-3} \cdot k\ (OH+\ CF_3CF=CH_2))^{-1}$ (Klöpffer and Wagner, 2007)

Because TFA was identified to be the relevant atmospheric degradation product, an assessment of the potential for photolytic degradation is considered beneficial to elucidate the concern of degradation in the environment.An opt-out registration dossier for polyhaloalkene contains the result from a QSAR estimate for indirect atmospheric degradation via OH-radicals. The utilized model AOPwin (v1.92) estimates an atmospheric half-life of 47 hours (24-hr day; OH-radical conc. 0.5e+06 /cm³).

Transformation product TFA

Indirect photochemical degradation of TFA in the troposphere is considered to be slow based on estimated OH radical reaction rates (

Table below), which corresponds to an atmospheric half-life of 30.85 d for the reaction with OH-radicals (24 h d^{-1}; OH radical concentration of $5 \cdot 10^5$ OH / cm^3). Comparing this half life with the criterion for long range transport potential (LRTP) of more than 2 days, a potential for LRT can be expected for TFA.

Table 9

Available OH reaction rate constants k(OH+CF3-COOH) of TFA and therewith calculated half life in air (T1/2 air)		
k(OH+$CF_3CF=CH_2$) [$cm^3\ mol^{-1}\ s^{-1}$]	**$T_{1/2\ air}$ [h]***	**Reference**
$0.52 \cdot 10^{-12}$	740.38	AOPwin
$1.4 \cdot 10^{-13}$	2750	(Klöpffer and Wagner, 2007)

* $T_{1/2\ air} = \ln 2 \cdot (5 \cdot 10^5\ OH\ radicals\ *\ cm^{-3} \cdot k\ (OH+\ CF3\text{-}COOH))^{-1}$ (Klöpffer and Wagner, 2007)

[8] Stockholm Convention on Persistent Organic Pollutants. United Nations Environment Programme, Geneva, Switzerland (http://chm.pops.int/)

Both information sources show that the photolytic degradation of TFA will be not as fast as the photolytic degradation of polyhaloalkene. The estimated half-life of TFA in air is expected to be two to eight times longer than the half-life of polyhaloalkene.

In conclusion, the results show that photolytic degradation and transformation to TFA is a relevant process for removal of polyhaloalkene from the environment. Both substances show half lives in air of at least close to or above 48 hours and therefore both substances are subject for atmospheric long-distance transport processes which can reach remote areas (for further information please see section 7.8.2.3 on environmental distribution modelling).

Phototransformation in water

The eMSCA considers data-waiving by the registrant as conclusive: the substance's properties will lead to immediate evaporation into atmosphere due to the low water solubility and the high vapour pressure resulting in a high air-water partitioning coefficient.

Phototransformation in soil

Likewise, the eMSCA considers data-waiving by the registrant as conclusive: the substance's properties will lead to immediate evaporation into atmosphere because of the high vapour pressure and the low adsorption potential to organic matter.

7.8.1.2 Biodegradation

Screening tests

Two tests were performed. One test (2008) is flagged as key study (reliability 1), another test is labelled with reliability 3 (not reliable). Under aerobic conditions less than 5% of polyhaloalkene was degraded after 28 days in the key study. The registrant concluded that polyhaloalkene is not ready biodegradable. The biodegradation study from 2007 was evaluated already in 2007 by the Belgian CA in the framework of NONS notification and amended in 2008. The Belgian CA agreed with registrants' (notifiers) discussed results and conclusion.

An opt-out registration dossier for polyhaloalkene contains the result from a test on ready biodegradation according to test guideline OECD 301D (Kurume 2010a). At the end of the test period of 28 days, only 2 percent mineralisation (measured parameter: oxygen consumption) were observed. It was concluded that no biodegradation was observed in the test.

The eMSCA considers the assessment by the registrants as conclusive.

Additional remark for TFA

The results of standard respiration tests with activated sludge showed that TFA is not readily biodegradable. Also, in tests on inherent biodegradation and in non-standard tests using several bacterial strains and different substrates, TFA was not degraded under aerobic conditions. Moreover, one field study investigated the degradation of TFA in field aquatic microcosms and laboratory sediment water systems. The substance was extremely persistent and showed no degradation during one-year field studies and 2880 h in laboratory microcosms. Only a non-assignable test showed some potential of biodegradation under anaerobic conditions.

The registrant concluded that TFA is persistent. This assessment is regarded as conclusive by the eMSCA.

Simulation tests (water and sediments)

No simulation test for polyhaloalkene in water or sediments is available. The eMSCA considers the data-waiving by the registrant is conclusive because the direct and/or indirect exposure to sediment is negligible.

Summary and discussion of biodegradation in water and sediment

Polyhaloalkene was not readily biodegradable in a screening test (<5% after 28 d) indicating that the substance is persistent in water. Simulation studies were not performed as the substance is highly volatile and predominantly will evaporate into the atmosphere within a short time.

Biodegradation in soil

No simulation test for polyhaloalkene in soil is available. The eMSCA considers the data-waiving by the registrant as conclusive because direct and/or indirect exposure into the soil is negligible.

7.8.1.3 Summary and discussion on degradation

The results show that degradation in the atmosphere will take some time and therefore polyhaloalkene might be subject to atmospheric long-distance transport processes which can reach remote areas.

Abiotic degradation occurs with polyhaloalkene as it is removed by oxidation in the air in 10 d. For indirect atmospheric degradation via OH-radicals, a QSAR estimate predicted an atmospheric half-life of 47 hours. In water, the substance is expected to be stable as the substance contains no hydrolysable functionalities.

Biotic degradation is not relevant for transformation of polyhaloalkene. This conclusion can be drawn because on the one hand the substance predominantly will end up in the atmosphere as result of its physical-chemical properties, and on the other hand the substance was identified being not readily biodegradable from results ofdifferent screening tests (best result: <5% after 28 d). Simulation studies were not performed.

7.7.2. Environmental distribution

7.8.2.1 Adsorption/desorption

The adsorption study was waived by the registrant with regard to the low adsorption potential (log K_{OW} < 3) and that the substance is a gas. These arguments are conclusive because it would be technically not feasible or very difficult to carry out a measurement e.g. with a HPLC UV detector and the relevance of the measured value would be limited in any case, since movement in soil or sediments would be strongly influenced by the (dis-) continuous gas phase.

The assessment of adsorption/desorption was evaluated in 2007 by the Belgian CA in the framework of NONS notification. The Belgian CA agreed with the results provided by the registrants (notifiers). This conclusion is not challenged by the eMSCA.

An opt-out registration dossier for polyhaloalkene contains the result from a test according to guideline OECD 121 (HPLC method). By the results of this measurements, the adsorption coefficient organic carbon/water (K_{OC}) was estimated to being lower than 18 L/kg or log K_{OC} <1.26 (Notox 2010).

On basis of this information the eMSCA expects that the substance will have a low tendency to adsorp to soil or sediments.

7.8.2.2. Volatilisation

No information was provided by the registrants at the time of the substance evaluation. Therefore, the eMSCA calculated the Henry's Law constant according to equation R.16-4 from the "Guidance on information requirements and Chemical Safety Assessment: Chapter R. 16: Environmental Exposure Estimation" (European Chemicals Agency, 2010) based on vapour pressure, molecular weight and water solubility (measured values each) results in a value of 2.23e+05Pa·m³·mol^{-1} indicating that the substance is highly volatile when emitted to aqueous media.

A result from a QSAR estimate for the Henry's Law Constant by applying the QSAR HENRYWIN (v3.20) was provided in a registration update after the initial evaluation period. For polyhaloalkane the model estimates:

Henry's Law constant = 1.48e+05 Pa*m³*mol^{-1}.

7.8.2.3. Distribution modelling

No information for the expected environmental distribution was provided by the registrant.

Long range transport potential

Model calculations using the OECD LRTP Screening Tool (OECD, 2006) indicate that there is a concern for long range transport (LRT) of the substance. The model requires only few input parameters: the partition coefficients octanol/water (K_{OW}), the dimensionless Henry's Law Constant (K_{aw}) and the environmental degradation half-lives in air, water and soil. Available measured OH reaction rate constants k(OH+$CF_3CF=CH_2$) for polyhaloalkene were used to calculate the half life in air (see Table in section 7.1.1.1). Regarding the degradation in water and soil only screening tests are available which show that polyhaloalkene is not readily biodegradable. The model, however, requires discrete values for simulation. Therefore, the half-lives according to the REACH Guidance Document R.16: Environmental Exposure Estimation (European Chemicals Agency, 2010) for inherent biodegradation in water of 150 d and 300 d in soil (tables R.16-5 and R.16-6, respectively) have been used in the first calculation. In addition, calculations with shorter half lives for water and soil have been carried out to show the influence of these half lives on the long-range transport potentials of polyhaloalkene (please see The calculated Characteristic Travel Distance of polyhaloalkene exceeds the LRTP criteria line (CTD: 5096.73 km), which is derived from model results for reference chemicals that are known as persistent organic chemicals ("POP-like"). Once released to the environment, polyhaloalkene will be transported via air for more than several thousand kilometres and will also be distributed to remote areas like the Alps. The results of the calculated Characteristic Travel Distance for the four scenarios mentioned above are displayed in the table below.

Table for the different scenarios used for calculation of LRTP).

The calculated Characteristic Travel Distance of polyhaloalkene exceeds the LRTP criteria line (CTD: 5096.73 km), which is derived from model results for reference chemicals that are known as persistent organic chemicals ("POP-like"). Once released to the environment, polyhaloalkene will be transported via air for more than several thousand kilometres and will also be distributed to remote areas like the Alps. The results of the calculated Characteristic Travel Distance for the four scenarios mentioned above are displayed in the table below.

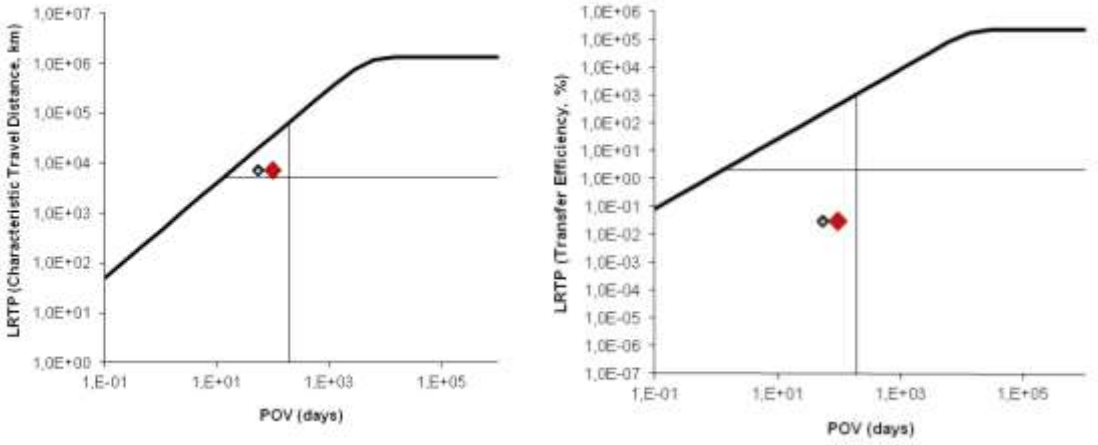
Table 10

Polyhaloalkene - input parameters and characteristic Travel Distance (CTD) of polyhaloalkene as results of different scenarios as calculated by the LRTP Screening Tool (OECD, 2006).				
Input parameter	**Scenario 1***	**Scenario 2****	**Scenario 3*****	**Scenario 4******
$logK_{OW}$	2.00	2.00	2.00	2.00
$logK_{aw}$	2.14	2.14	2.14	2.14
$T_{1/2\ air}$ [h]	350	350	343.75	347.16
$T_{1/2\ water}$ [h]	3600	1200	1200	1200
$T_{1/2\ soil}$ [h]	7200	2160	2160	2160
CTD [km]	7232.19	7232.17	7103.7	7173.78

* Klöpffer and Wagner, 2007; assumed high half life in water and soil; ** Klöpffer and Wagner 2007; assumed lower half life in water and soil; *** Papadimitriou et al., 2008; **** Orkin et al., 2010.

The characteristic travel distance and overall persistence (Pov) was calculated by the LRTP Screening Tool (OECD, 2006) and respective criteria lines. These are derived from model results for reference chemicals that are known as persistent organic chemicals.

Figure 1: Characteristic travel distance and overall persistence (left) and transfer efficiency and overall persistence (right) for polyhaloalkene



The transfer efficiency and overall persistence P_{ov} were calculated by the LRTP Screening Tool (OECD, 2006).

Additional information for TFA

Due to the volatility of polyhaloalkene, TFA was identified to be the relevant degradation product of polyhaloalkene in the atmosphere (please see section 7.8.1.1 on "phototransformation in air").

There is only one measured OH reaction rate constant k(OH+CF_3-COOH) available for TFA. Consequently, a calculated reaction rate constant was additionally used to calculate the half-life in air (**Error! Reference source not found.**).

Table 3

TFA - input parameters and characteristic Travel Distance (CTD) of TFA as results of different scenarios as calculated by the LRTP Screening Tool (OECD, 2006).							
Input parameter	**TFA_1**	**TFA_2**	**TFA_3**	**TFA_4**	**TFA_5**	**TFA_6**	**TFA_7**
$logK_{OW}$	–2.10	–2.10	**-0.5**	**0.5**	0.5	0.5	0.5
$logK_{aw}$	–2.147*	–**3.41****	–3.41**	–3.41**	–3.41**	–**2.147***	–2.147*
$T_{1/2\ air}$ [h]	740.38	740.38	740.38	740.38	740.38	740.38	**2750**
$T_{1/2\ water}$ [h]	3600	3600	3600	3600	**7200**	7200	7200
$T_{1/2\ soil}$ [h]	7200	7200	7200	7200	**72000**	72000	72000
CTD [km]	12710.59	5222.86	5222.86	5222.81	6152.94	13515.74	37768.18

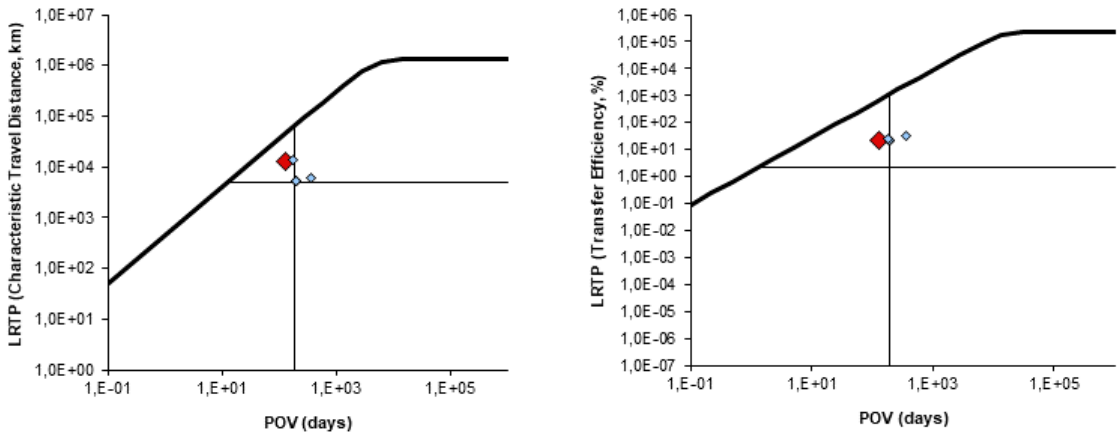
* measured value ** calculated value

Regarding the degradation in water and soil, only screening tests are available which show that TFA is not inherently biodegradable. The model, however, requires discrete values for simulation. Due to this fact the half-lives for biodegradation in water of 300 d and 3000 d in soil (tables R.16-5 and R.16-6 respectively) have been used according to the REACH Guidance Document R.16: Environmental Exposure Estimation (European Chemicals Agency, 2010). In addition, calculations with shorter half-lives for water (150 d) and soil (300 d) have been carried out to show the influence of these half-lives on the long-range transport potentials of TFA.

The calculated LRTP of TFA exceed the LRTP criteria line (CTD of 5096.73 km;

Figure), which is derived from model results for reference chemicals that are known as persistent organic chemicals ("POP-like"). Especially if TFA is released to air, it will be transported via air for more than several thousand kilometers which stands out in the CTDs for scenarios TFA_1, TFA_6 and TFA_7.It has to be kept in mind that the calculated values only apply for TFA in the atmosphere. The long range transport potential in the aquatic compartment is much lower (CTD < 600 km).

Figure 2: Characteristic travel distance and overall persistence (left) and transfer Efficiency and overall persistence (right) of TFA



The characteristic travel distance and overall persistence (P_{ov}) as well as the transfer efficiency of TFA were calculated by the LRTP Screening Tool (OECD, 2006) and respective criteria lines. These are derived from model results for reference chemicals that are known as persistent organic chemicals.

Conclusion

The assumed potential for long range transport (LRTP) of polyhaloalkene and TFA is confirmed by model calculations using the OECD LRTP Screening Tool (OECD, 2006).

For the two required partition coefficients (of polyhaloalkene and TFA respectively) different values are available (The calculated Characteristic Travel Distance of polyhaloalkene exceeds the LRTP criteria line (CTD: 5096.73 km), which is derived from model results for reference chemicals that are known as persistent organic chemicals ("POP-like"). Once released to the environment, polyhaloalkene will be transported via air for more than several thousand kilometres and will also be distributed to remote areas like the Alps. The results of the calculated Characteristic Travel Distance for the four scenarios mentioned above are displayed in the table below.

Table and **Error! Reference source not found.**, respectively). Consequently, their impact on the LRTP estimation was assessed. A measured and an estimated log Kaw are available. The available log K_{OW} values widely range between –2.1 and 1.35. During calculation of the LRTP it became obvious that use of log K_{aw} strongly effects the result for the CTD while using the log K_{OW} only has little impact.

The model calculations using the OECD LRTP Screening Tool (OECD, 2006) underline the assumption that both polyhaloalkene and TFA as its environmentally relevant degradation product fulfil the criteria for substances with long range transport potential according to criteria of the Stockholm Convention on Persistent Organic Pollutants. This outcome alone does not automatically qualify the two substances as POPs.

7.8.2.4. Summary and discussion of environmental distribution

The registrant provided the conclusion that based on the physical-chemical properties polyhaloalkene is expected to distribute mainly in the atmospheric compartment when released to the environment.

There is no information on the tendency for volatilisation from aqueous media available in the registration dossier and no distribution modelling was carried out supporting the registrants assumption that the majority of polyhaloalkene will end up in the atmosphere when released to any environmental compartment.

In context of the substance evaluation process, additional examinations regarding the environmental distribution and fate of polyhaloalkene and his environmentally relevant transformation product TFA were carried out. These examinations lead to the conclusion that both substances will distribute easily within the environment and have a high potential for long range transport. The eMSCA considers that there are no additional indications for substance properties leading to the need for an identification of polyhaloalkene as SVHC according to Article 57 (f) REACH.

7.7.3. Bioaccumulation

7.7.3.1. Aquatic bioaccumulation

In accordance with the REACH Annex IX, the bioaccumulation study is waived because the substance can be expected to have a low potential for bioaccumulation (log K_{OW} is 2.0).

The assessment by the registrant is regarded as conclusive by the eMSCA.

Additional remark with regard to the relevant degradation product TFA

In accordance with the REACH Annex IX, the bioaccumulation study for TFA is waived because the substance can be expected to have a low potential for bioaccumulation (log K_{OW} is 0.79).

The assessment by the registrant is regarded as conclusive.

7.7.3.2. Terrestrial bioaccumulation

No information available in the registration. The data-waiving by the registrant is considered as conclusive because direct and/or indirect exposure into the soil is negligible.

7.7.3.3. Summary and discussion of bioaccumulation

It can be expected that the substance has a low potential for bioaccumulation. This appraisal is based on the Octanol-Water-Partition Koefficient (log K_{OW} = 2.0). A BCF value is not available.

Additional remark with regard to TFA

It can be expected that the environmentally relevant degradation product TFA has a low potential for bioaccumulation. This appraisal is based on log K_{OW} of 0.79. An experimental BCF value is not available.

7.7.4. Secondary Poisoning

Due to the low log K_{OW} value (see above), secondary poisoning is not considered as relevant.

7.8. Environmental hazard assessment

A possible or suspected toxic effect of the substance on the species of the different compartments and trophic level is not an object of the initial concern. The check of the end points gave no indications to additional concerns.

However, an overview of the checked endpoints is provided here to support the statements of the PNEC derivation at this point and the conclusion for classification and labelling.

Table 12 (studies are available at ECHA dissemination site, unless stated otherwise)

Ecotoxicological information on polyhaloalkene			
Endpoint	**Value**	**Source**	**Remarks**
Aquatic toxicity			*PNEC can be derived:* *Freshwater: 0.25 mg/L* *Marine: 0.025 mg/L* *Intermittend release:* 0.33 mg/L
fish short-term	96h-LC_{50} > 197 mg/L	96-Hour acute toxicity in *Cyprinus carpio* with HFO-1234yf (static) according to test guideline OECD 203 (TNO 2006c)	
	96h-LC_{50} = 33 mg/L	96-Hour acute toxicity in *Oryzias latipes* with HFO-1234yf (semi-static) according to test guideline OECD 203 (Kurume 2010b)	Used for the derivation of PNEC: AF: 100
fish long term	28d NOEC = 2.7 mg/L	28-day long term Toxicity in *Cyprinus carpio* according to test guideline OECD 215 (Notox 2011a)	
daphnia short-term	48h-EC_{50} > 100 mg/L	acute toxicity in *Daphnia magna* with HFO-1234yf according to test guideline OECD 202 (TNO 2006d)	
	48h-EC_{50} = 65 mg/L	acute toxicity in *Daphnia magna* with HFO-1234yf (static) according to test guideline OECD 202 (Kurume 2010c)	
daphnia long-term	21d-NOEC = 15,2 mg/L -	21-day long term Toxicity in *Daphnia magna* with HFO-1234yf (semi static) according to test guideline OECD 211 (Notox 2011b)	
Algae Freshwater	72h - ErC_{50} > 100 mg/L	Freshwater algal growth inhibition test with HFO-1234yf in *Pseudokirchneriella subcapitata* according to test guideline OECD 201 (TNO 2006e)	
	72h - ErC_{50} > 2.5 mg/L 72h – NOErC >= 2.5 mg/L	Freshwater algal growth inhibition test with HFO-1234yf (static) in *Pseudokirchneriella subcapitata* according to test guideline OECD 201 (Kurume 2010d)	Used for the derivation of PNEC: AF: 10
Algae marine	72h - ErC_{50} > 2.5 mg/L 72h – NOErC >= 2.5 mg/L	Freshwater algal growth inhibition test with HFO-1234yf (static) in *Pseudokirchneriella subcapitata* according to test guideline OECD 201 (Kurume 2010d)	Used for the derivation of PNEC: AF: 100
Toxicity to microorganisms			*waived*
No emission to STP expected			*No PNEC ca be derived*
Sediment toxicity			*waived*
PNEC was derived using the equilibriumpartitioning method (EPM) based on the PNECaqua			*Freshwater* *PNEC:* 1.35 mg/kg sediment dw *marine water* PNEC: 0.135 mg/kg sediment dw
Terrestrial toxicity			*waived*

Ecotoxicological information on polyhaloalkene			
Endpoint	**Value**	**Source**	**Remarks**
PNEC was derived using the equilibriumpartitioning method (EPM) based on the PNECaqua			*PNEC:* 0.72

As stated in section 7.8.1.1 "phototransformation in air", TFA as transformation product will be the result of degradation processes in the atmosphere (photolytic degradation). The complete environmental hazard assessment of TFA was not an object of the initial concern of the substance evaluation of polyhaloalkene.

However, an overview of the checked key endpoints is given to support the statements of the PNEC derivation and proposal for harmonised classification and labeling at this point.

Table 13 (studies are available at ECHA dissemination site, unless stated otherwise)

Ecotoxicological information on TFA			
Endpoint	**Value**	**Source**	**Remarks**
Aquatic toxicity			*PNEC: 0.56 mg/L*
fish short-term	96h-LC_{50} > 999 mg/L	The acute toxicity of sodium trifluoroacetate to the zebrafish *brachydanio rerio* according to OECD guideline 203 (Solvay Duphar, 1992a)	
fish long term	-		*waived*
daphnia short-term	48h-EC_{50} > 999 mg/L	The acute toxicity of sodium trifluoroacetate to *daphnia magna* according to test guideline OECD 201 (Solvay Duphar, 1992b)	
daphnia long-term	21d-NOEC ≥ 25 mg/L	Influence of 30% w/w Sodium trifluoroacetate aqueous solution to *Daphnia magna* in a Semi-static Reproduction Test according to test guideline OECD 211 (IBACON 2010)	
Algae (freshwater)	72h-ErC_{50} = 241.95 mg/L	Alga, Growth Inhibition Test Effect of the trifluoroacetic acid on the growth of *Pseudokirchneriella* subcapitata according to OECD guideline 201 (Ineris 2017)	Contained in registration update of 08/2018. Also considered by eMSCA.
	72h-NOEC = 2.5 mg/L 72h ErC_{10} = 5.6 mg/L		
Algae (freshwater)	72h-ErC_{50} = 8.5 mg/L	A comparison of the toxicity of sodium trifluoroacetate, difluoroacetic acid, sodium monofluoroacetate and sodium fluoride to the alga *selenastrum capricornutum*. (Solvay Duphar, 1995) Toxicity of sodium trifluoroacetate to the alga *Raphidocelis subcapitata*. (ELF ATOCHEM 1996)	geometric mean from 2 key studies
	72h-NOEC = 0.2 mg/L		
Algae (marine)	72h-ErC_{50} > 97 mg/L	The toxicity of sodium trifluoroacetate to the marine alga *Phaeodactylum tricornutum* according to guideline OECD 201. (Solvay Duphar 1993)	
	72h-NOEC = 97 mg/L		
Toxicity to microorganism			*No PNEC can be derived*
sediment toxicity			*waived*
terrestrial toxicity (plants)	28d - EC50 = 4.7 mg TFA/kg 28h-NOEC = 0.83 mg TFA/kg	Determination of effects of sodium trifluoroacetate in soil on seed germination and early plant growth of Sunflower *(Helianthus annuus)* and Mung Bean *(Phaseolus aureus).*	PNEC: 8.3 µg/kg soil dw

Ecotoxicological information on TFA			
Endpoint	**Value**	**Source**	**Remarks**
		(Brixham 1993)	

7.8.1. PNEC derivation and other hazard conclusions

7.8.1.1. PNEC derivation

The assessment by the registrant is considered conclusive by the eMSCA.

Additional remarks for TFA

A PNEC for microorganisms of 83.2 mg/L is derived by the registrant. This assessment is not conclusive. No toxicity was found in the key study. In the technical IUCLID Dossier the registrant pointed out that the 3-hour EC_{20} and EC_{50} are clearly higher than 1000 mg NaTFA/L (832 mg TFA/L) under the present test conditions and that the NOEC of sodium trifluoroacetate (NaTFA) may be established above 1000 mg/L (832 mg TFA/L). Therefore, no PNEC can be derived.

7.8.1.2. Conclusion on environmental hazard assessment

For polyhaloalkene, the check of the endpoints give no indications for environmental hazard. As no toxicity is observed, the eMSCA concludes that no classification is warranted for any environmental endpoint evaluated for the substance.

For the transformation product TFA the check of the endpoints confirms the assessment of the registrant. No acute toxic effects were observed for fish and neither acute nor long term effects were observed on daphnia. Therefore, long term test on fish can be waived.

TFA is toxic only for algae. A PNEC of 0.56 mg/L is derived on the basis of growth rate. The assessment by the registrant is considered as conclusive by the eMSCA.

In the updated CSR the registrant pointed out:

"*Conclusion on environmental classification*

Environmental official classification according to Annex VI of Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008: Trifluoroacetic acid is reported under the Index No 607-091-00-1 and is classified as Aquatic Chronic 3, H412. This official classification is conservative because, based on the key studies available, the substance should not be classified for the environment as explained below: Short-term E/LC50 values are available for algae (key study growth rate 72hEC50 = 237 mg/L), daphnia (48hEC50 > 100 mg/L) and fish (96hLC50 > 100 mg/L). All of the key studies demonstrate E/LC50 above 100 mg/L, showing that the substance does not need to be classified for acute toxicity to aquatic organisms according to the CLP and the UN-GHS criteria. Additionally, trifluoroacetic acid is not readily biodegradable and due to the log Kow < 4 there is no tendency to bioaccumulate. Chronic toxicity data are available for algae showing a 72h ErC10 of 5.6 mg/L and for daphnia showing a 21d NOEC above 25 mg/L. Therefore, the substance does not need to be classified for chronic toxicity to aquatic organisms according to the CLP and UN-GHS criteria."

The assessment by the registrant is considered conclusive by the eMSCA.

Additional remarks

It can be noted that the aquatic toxicity (fish and daphnia) tests were carried out as a limit test with trifluoroacetate sodium. The test concentration corresponded to the solubility from trifluoroacetate sodium in ISO-water. Stoichiometric correction which corresponds to the solubility of TFA in ISO-water have had to be used.

7.9. Human Health hazard assessment

General remark

Unless noted otherwise, the original study reports relevant to this section were available to the eMSCA. In all of the inhalation studies, unless otherwise noted, analytical concentrations were found to be within reasonable limits of the respective nominal values. Thus, for ease of reference, only the nominal concentrations are given. All concentrations in ppm are ppmV (i.e. v/v., eq. to µL/L or mL/m^3).

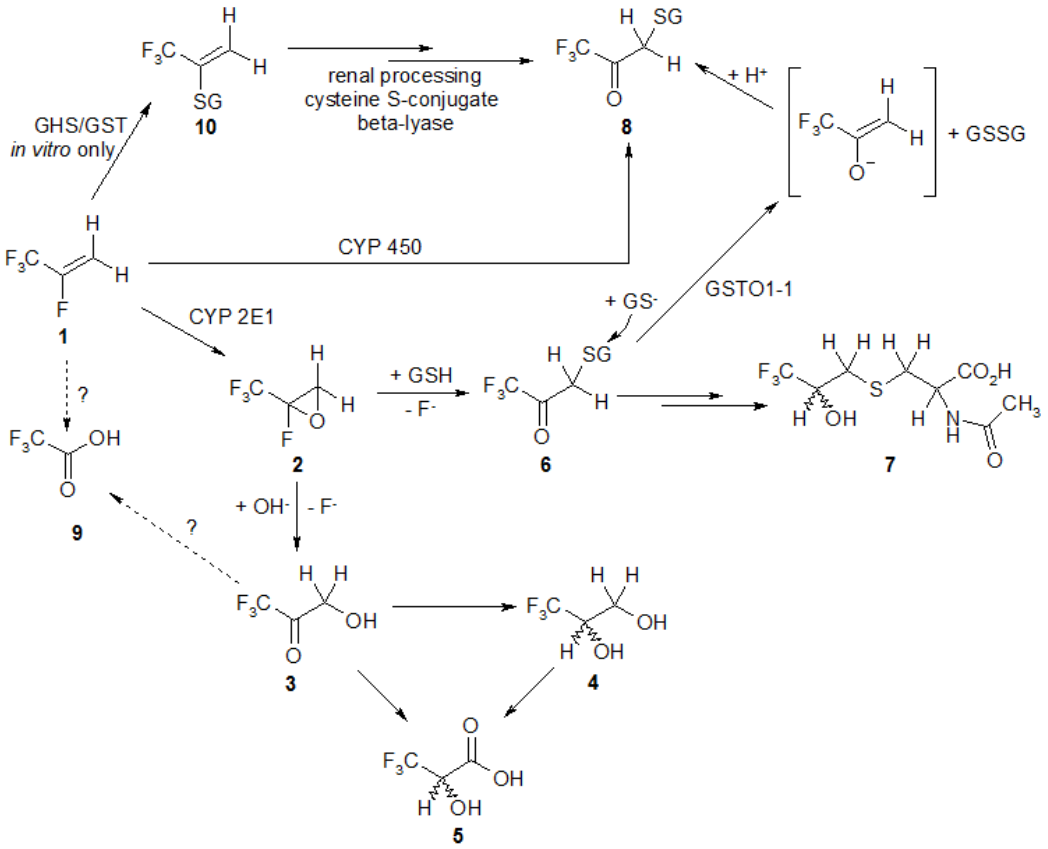
7.9.1. Toxicokinetics

An overview of the available studies and their main results is given in the Table on the next page. While the existing *in vivo* studies qualitatively demonstrate systemic uptake, no quantitative information of the degree of absorption and the subsequent relative distribution of polyhaloalkene in the body is available. Since polyhaloalkene is a gas, inhalation is the most relevant route of exposure.

The metabolites identified in rats *in vitro* and *in vivo* are shown in

Figure below.

Figure 3: Putative route of biotransformation of polyhaloalkene in rats (Schuster et al., 2008).



1: polyhaloalkene; **2**: 2,3,3,3-tetrafluoro-1,2-epoxypropane; **3**: 3,3,3-trifluoro-1-hydroxyacetone; **4**: 3,3,3-trifluoro-1,2-dihydroxypropane; **5**: 3,3,3-trifluorolactic acid; **6**: S-(3,3,3-trifluoro-2-oxo-propyl)glutathione; **7**: N-acetyl-S-(3,3,3-trifluoro-2-hydroxypropyl)-L-cysteine; **8**: 3,3,3-trifluoroacetone; **9**: trifluoroacetic acid

Table 14

OVERVIEW OF AVAILABLE ADME STUDIES WITH POLYHALOALKENE					
Method/ guideline	**Species, strain, sex, no/group**	**Scenario; dose levels (ppm); exposure duration**	**Results**	**Remarks**	**Reference**
In silico					
PBTK modelling of arterial blood levels; reliability: 4 (not assignable)	Adult female humans, pregnant rabbits and rats	Scenario 1: Acute exposure adult female human, simulation for 8 h; 80000; 0.5 – 5 min Scenario 2: Occupational exposure of adult female human; 400; 6 -8 h/d, 1 d or 1-4 "work weeks" Scenario 3: Repeated exposure of pregnant rabbit; 4000; 1 or 6 h/d for 1/14/28 d Scenario 4: Repeated exposure of rat; 50000; 1 or 6 h/d for 1/14/28 d	The following steady state concentrations also the peak concentrations) in arterial blood were predicted: Scenario 1: 14.2 mg/L Scenario 2: 0.0709 mg/L Scenario 3: 1.342 mg/L Scenario 4: 17.71 mg/L Rapid uptake and elimination from arterial blood, linear correlation of AUC with time	None	(DuPont, 2008)
In vitro					
Biotransformation study, no specific guideline:reliability 2 (reliable with restrictions)	Rat (Sprague-Dawley) liver micro-somes (naïve or induced for CYP2E1); human S9 fraction	Incubation for up to 1 h at 37°C, in the presence or absence of NADPH; final concentration not reported	No fluorine-containing metabolites detected in the absence of NADPH; with NADPH, GSH conjugates of parent and breakdown products, profiles qualitatively similar between species, with relative proportions of individual metabolites varying	None	(Schuster et al., 2008)
Biotransformation study, no specific guideline; reliability 2 (reliable with restrictions)	Liver microsomes (rabbit), with and without NADPH	Incubation with GSH, duration and final polyhaloalkene concentration not reported	No fluorine-containing metabolites detected in the absence of NADPH; with NADPH, GSH conjugates of breakdown products detected	None	(Schuster et al., 2010)

OVERVIEW OF AVAILABLE ADME STUDIES WITH POLYHALOALKENE					
Method/ guideline	**Species, strain, sex, no/group**	**Scenario; dose levels (ppm); exposure duration**	**Results**	**Remarks**	**Reference**
Determination of tissue/air partition coefficients (PCs); reliability 2 (reliable with restrictions)	Rat (F) and rabbit (M): blood, liver, muscle, fat; Human (M/F): blood	Analysis by headspace gas chromatography following incubation; 10000; 3 h	Tissue-to-Air partition coefficients (PCs, mean ± SD; n = 5): Rat (F): Blood: 0.076 ± 0.010; muscle: 0.089 ± 0.033; fat: 0.957 ± 0.332; liver: 0.031 ± 0.011 Rabbit (M): Blood: 0.072 ± 0.010; muscle: 0.047 ± 0.016; fat: 1.599 ± 0.259; liver: 0.061 ± 0.021 Human (F): Blood: 0.038 ± 0.007 Human (M): Blood: 0.035 ± 0.005	None	(DuPont, 2011)
In vivo (inhalation)					
Biotransformation study, no specific guideline; reliability 2 (reliable with restrictions)	Rat, Sprague-Dawley, M, n=5 Induced for CYP2E1 by administration of pyridine for 5 d prior to test Mouse, B6C3F1, M, n=5	Single exposure, 2000 - 10000 - 50000; 6 h Single exposure; 50000; 3.5 h	Indication of CYP2E1 being the primary enzyme involved in the oxidative biotrans-formation of polyhaloalkene; main (urinary, fluorine containing) metabolite: N-acetyl-S-(3,3,3-trifluoro-2-hydroxy-propyl)-L-cysteine. For further minor metabolites cf. Figure . 90% of mercapturic acid derivatives removed from the urine within 18 (rat) or 24 (mice) hours post-exposure Metabolic profile similar to that of rats. Some additional minor signals which were not investigated further	Not a complete biotransformation study: Only fluorine-containing urinary metabolites were assessed, while other excreta and non-fluorine-containing metabolites were not. As a result, no quantitative mass balance could be obtained.	(Schuster et al., 2008)
Biotransformation study, no specific guideline followed; reliability 2 (reliable with restrictions)	Rabbit, NZW, F, n=3	Single exposure; 2000 – 10000 – 50000; 6 h	Qualitative and quantitative differences in metabolism in rats vs. mice. The following metabolites were not detected in rabbit urine: 3,3,3-trifluoro-1-	Not a complete biotransformation study: Only fluorine-containing urinary metabolites	(Schuster et al., 2010)

OVERVIEW OF AVAILABLE ADME STUDIES WITH POLYHALOALKENE					
Method/ guideline	**Species, strain, sex, no/group**	**Scenario; dose levels (ppm); exposure duration**	**Results**	**Remarks**	**Reference**
			hydroxyacetone, 3,3,3-trifluorolactic acid, and trifluoroacetic acid. Clearance of the largest part of main metabolite and inorganic fluorine within 12 h post-exposure, but at the high-dose level	were assessed, while other excreta and non-fluorine-containing metabolites were not. As a result, no quantitative mass balance could be obtained.	
Acute inhalation toxicity study, equivalent or similar to OECD 403, Additional investiga-tion into urinary metabolites Reliability 2 (reliable with restrictions)	Rabbit, NZW, M+F+F presumed pregnant (GD 12)	Single exposure on presumed GD 12, followed by 14 d post-exposure observation period; 0 - 50000 - 100000; 1 h	Main metabolites: S-(3,3,3-trifluoro-2-hydroxypropanyl)-mercaptolactic acid and N-acetyl-S-(3,3,3-trifluoro-2-hydroxypropanyl)-L-cysteine No differences in metabolism established between non-pregnant and presumed pregnant females *Acute toxicity results: see section 7.9.2.2*	Not a complete biotransformation study: Only fluorine-containing urinary metabolites were assessed, while other excreta and non-fluorine-containing metabolites were not. As a result, no quantitative mass balance could be obtained.	(Huntingdon, 2011; Schmidt et al., 2012)

In vitro tests with liver microsomes suggest that oxidative biotransformation of polyhaloalkene in rats is predominantly catalysed by CYP2E1 (Schuster et al., 2008). Established or hypothesised transformation reactions include (ep-)oxidation of the double bond and cleavage of C-F bonds to yield inorganic fluoride. Glutathione (GSH) conjugation of breakdown products was demonstrated by evidence of the respective conjugates. Direct conjugation of the parent with glutathione was seen only to a small extent in the *in vitro* experiment, whereas no corresponding signals were detected *in vivo*. This was interpreted by the study authors as a sign of low reactivity of polyhaloalkene towards GSH. *In vitro*, several GSH conjugation products were identified, their relative amounts varying slightly between the species investigated (rat, rabbit, mouse, human).

Among the metabolites given in

Figure , *N*-acetyl-S-(3,3,3-trifluoro-2-hydroxy-propyl)-L-cysteine (M7) was the one predominantly found in urine. Urinary levels of this compound peaked between 0-6 h following exposure and 90% of these peak levels were removed by 18 h (rat) or 24 h (mice) post-exposure. For other minor metabolites including 3,3,3-trifluorolactic and trifluoroacetic acid, cf. Figure 3. Detection of unchanged parent in urine was not reported.

At 50000 ppm, the metabolic profile established in mice was comparable to that found in rats.

In light of the low amount of recovered metabolites (as compared to the calculated total dose), the study authors concluded that *"[…] most of the inhaled R-1234yf is expected to be rapidly exhaled due to its low boiling point"* (Schuster et al., 2008).

However, in the view of the eMSCA it is not possible to draw this conclusion from the experiment as a complete mass balance is not available and other routes of elimination (faeces, bile, exhalation) or even accumulation of polyhaloalkene in the body of the test animals were not investigated.

In 2010, authors from the same group also investigated the biotransformation of polyhaloalkene in rabbits (Schuster et al., 2010). Qualitative and quantitative differences in comparison with the metabolism of rats and mice were established (for details see original publication, cf. also

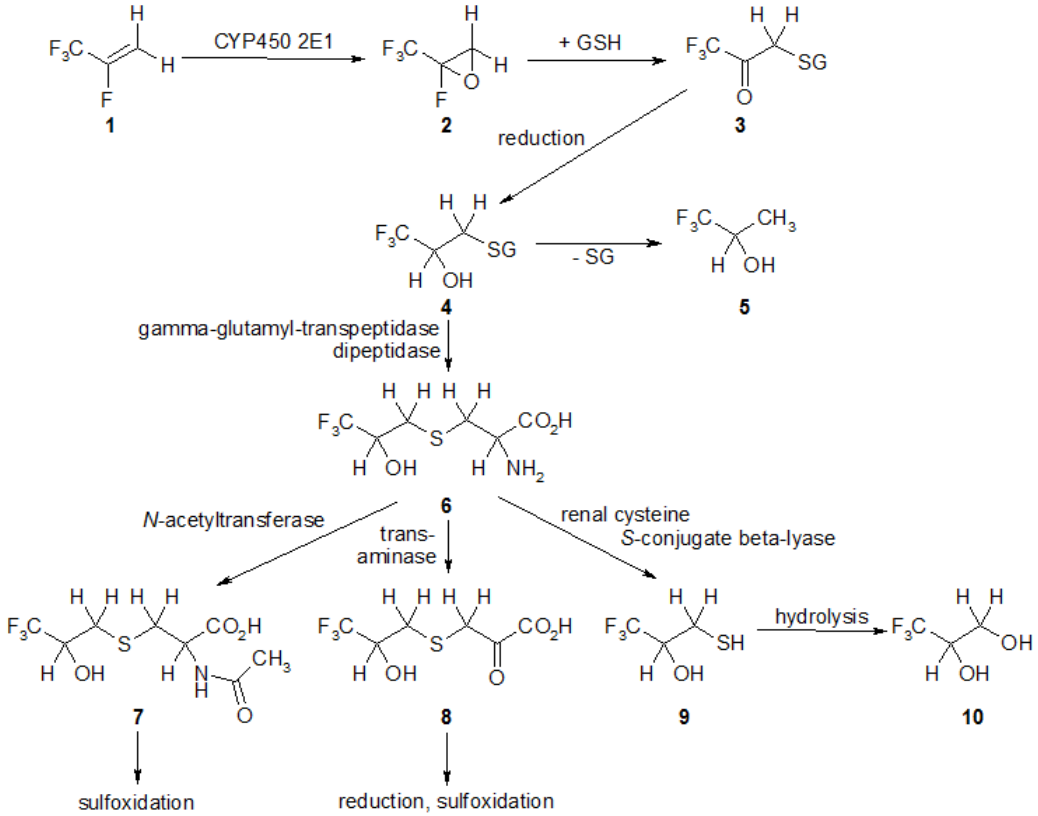
Figure 4. Note that in contrast to

Figure , only measured, but not hypothesised metabolites are given).

Another investigation of the biotransformation of polyhaloalkene in rabbits was performed within the frame of an acute inhalation experiment (Huntingdon, 2011; Schmidt et al., 2012). Predominant metabolites were S-(3,3,3-trifluoro-2-hydroxypropanyl)-mercaptolactic acid and N-acetyl-S-(3,3,3-trifluoro-2-hydroxypropanyl)-L-cysteine, whose signal intensities in ^{19}F-NMR spectra represented more than 78% of total ^{19}F-related signals in all analysed urine samples.

Quantification of the test substance's mercapturic acid conjugates by LC/MS-MS showed no significant difference in the mean recovery of this metabolite excreted in urine within 48 h between non-gravid (43.11 ± 22.35 µmol) and pregnant (50.47 ± 19.72 µmol) female rabbits. With the exception of one yet unidentified metabolite (12-17% of the main metabolites in female rabbits and < 7% in male rabbits), no differences in urinary metabolite pattern or quantity of excreted metabolites were observed between the different groups.

Figure 4: Biotransformation of polyhaloalkene in rabbits (Schuster et al., 2010)



Physiologically based toxicokinetic (PBTK) modelling was applied to a set of different scenarios in adult female humans, pregnant rabbits, and rats (DuPont, 2008). The scenarios for which modelling in the different species has been performed vary with respect to both assumed exposure dose levels and exposure time and thus hardly allow for interspecies comparison. In addition, a high sensitivity of the model with respect to the parameter blood-air partition coefficient (PC) was demonstrated: According to the authors, variation of PC by 1% resulted in a change of approximately 1% in the arterial blood concentration, indicating that the model was linearly proportional to this parameter. The PC values used for modelling were derived from an *in vitro* test only (DuPont, 2011), which in itself already introduces an element of uncertainty to the PC estimation. Furthermore, in this study, relative standard deviations for the individual PC estimates ranged from 13 to 35% (cf. Table above).

Finally, in (DuPont, 2011), no information on the validation of the model parameters used against any real-life data for other substances is reported. All in all, the plausibility of the predicted results cannot be assessed and, consequentially, its results cannot be used to draw conclusions with relevance to the risk assessment under question and can only remain speculative.

7.9.1.1. Summary and discussion of toxicokinetics

Experimental data are available on the biotransformation of polyhaloalkene in liver microsomes from rats, mice, rabbits, and humans *in vitro* and on the biotransformation and urinary excretion of polyhaloalkene in rats, mice, and rabbits *in vivo*.

However, a full ADME (absorption, distribution, metabolism, and excretion) study, including a complete mass balance following uptake of polyhaloalkene into the mammalian organism, is not available. Furthermore, only a partial, qualitative picture of mammalian metabolism is obtained, as no investigation was performed with regard to the spectrum of metabolites in other excreta (faeces, exhaled air) and to potential metabolites not containing fluorine. Likewise no data on bioaccumulation in mammals or on ADME following repeated administration have been generated.

7.9.2. Acute toxicity

7.9.2.1. Acute toxicity: oral

Due to the evaluated substance being a gas at room temperature and ambient pressure, no studies with oral administration are available.

7.9.2.2. Acute toxicity: inhalation

Three studies on acute inhalation toxicity are available for polyhaloalkene (Table 4).

Following 4 h exposure of rats to polyhaloalkene to concentrations of 200000 or 400000 ppm, no mortality occurred (TNO, 2006a). During the second half of the exposure period (i.e. first observed 2 h after the start of the study), breathing impairment (decreased breathing rate and, at the high dose level, laboured breathing) was noted in both dose groups. Notably, in the Gradient phase III study report (Gradient, 2009b), the decrease in breathing rate in the rat study is termed an 'anaesthetic effect' which could be interpreted as pointing to a neurotoxic mode of action. However, the original study authors did not use this terminology, and in the view of the eMSCA there is no further evidence to support (or refute) this conclusion.

In the high-dose groups, body weight gain until day 7 of the post-exposure period was only 80/88% of that observed in the male/female low dose groups, ultimately resulting in reduced terminal body weight. For males, reduced body weight gain was primarily observed during days 0-7, whereas for females it was more evenly spread over the complete exposure and post-exposure periods. Due to lack of an untreated control group, a potential influence of polyhaloalkene on body weight gain and terminal body weight of the low dose groups cannot be assessed.

Macroscopical pathology evaluation showed grey discolouration of the lung in 1/1 and 3/1 of the animals of the male/female low and high dose groups, respectively, as well as singular incidences of a red discoloured spot in one male and a petechia in one female of the low dose groups. An overview of the findings in the rat study is given in Table 56.

Table 45

OVERVIEW OF AVAILABLE ACUTE INHALATION TOXICITY STUDIES WITH POLYHALOALKENE					
Method/ guideline	**Species, strain, sex, no/group**	**Scenario; dose levels (ppm); exposure duration**	**Results**	**Remarks**	**Reference**
Acute toxicity study (range-finder)/similar to OECD 403 (cf. 'Remarks' column); GLP*; reliability 2 (reliable with retstrictions)	Mouse, CD-1, M/F, 2	Single exposure, 7 d post-exposure observation period; 20000 -100000; 4 h	No mortality at the highest dose tested; LC_{50} > 100000 ppm Laboured breathing in 50/100% of the animals at 20000/ 100 000 ppm first noted 3 h into exposure (both dose levels), but not post-exposure Yellow anogenital staining in males on days 5-7/2-7 d post-exposure (20000/100 000 ppm) **NOAEC**: < 20000 ppm	Only range-finding study, number of animals lower than requested by OECD TG 403	(Huntingdon, 2004)
Acute inhalation toxicity study/OECD 403; GLP; reliability 1 (reliable without restrictions)	Rat, Sprague-Dawley SPF, M/F, 5	Single exposure, 14 d post-exposure observation period; 0 - 200000 - 400000; 4 h	Mortality No mortality at the highest concentration tested; LC_{50} > 400 000 ppm Clinical signs: Slightly decreased breathing rate first noted 2 h into exposure (both dose levels, high-dose: also laboured breathing), but not post-exposure Body weight: Ca. 10% reduction in high vs. low dose males Gross pathology: Lungs: grey, discoloured (both groups), red discoloured spot, petechia (lower dose group only) **NOAEC**: < 200000 ppm	None	(TNO, 2006a)

OVERVIEW OF AVAILABLE ACUTE INHALATION TOXICITY STUDIES WITH POLYHALOALKENE					
Method/ guideline	**Species, strain, sex, no/group**	**Scenario; dose levels (ppm); exposure duration**	**Results**	**Remarks**	**Reference**
Acute inhalation toxicity study/OECD 403; GLP*; reliability 4 (not assignable)$	Rat, Crl:CD(SD), M/F, 5	Single exposure; 0 - 19 700; 4 h	No mortality, no test material-related clinical signs, no effect on body weight LC_{50} > 20 000 ppm	None	Unknown, 2010$
Two-phase screening study, no guideline; GLP* (except for metabolite analysis)	Rabbit, NZW Phase 1: 1 F (non-pregnant) + 1 F (presumed pregnant) Phase 2: a) 5 M/group; b) 5 F (non-pregnant)/ group; c) 6 F (presumed pregnant)/ group	Phase 1: Single exposure on (presumed) GD 12, 2 d post-exposure observation period; 100000; 1 h; Phase 2: Single exposure on (presumed) GD 12, 14 d post-exposure observation period; 0 - 45000 (a only) -50 000 (c only) - 100000; 1 h	Phase 1: No effects on viability, clinical signs, or body weight Phase 2: No effects on viability, clinical signs, body weight, macroscopic and microscopic (heart, kidneys, liver, lungs) pathology **NOAEC**: 100000 ppm	No pathology evaluation of phase 1 Metabolites cf. toxico-kinetics section	(Huntingdon, 2011)

* Claimed but no certificate available for this evaluation; $ The test is summarised on ECHA's dissemination site as being part of an opt-out registration dossier. No bibliographic information about this reference is available, and hence, its reliability cannot be assessed.

Table 5

OVERVIEW OF THE FINDINGS IN THE ACUTE 4 H INHALATION STUDY WITH POLYHALOALKENE IN RATS (TNO, 2006A)				
Sex	**Males (5/group)**		**Females (5/group)**	
Dose level (ppm)	**200000**	**400000**	**200000**	**400000**
Body weight data (g, mean ± SD)				
Terminal body weight, day 14	306.1 ± 10.9	273.6 ± 9.2	214.2 ± 4.3	205.1 ± 4.9
Body weight gain, days 0-7	41.3 ± 9.2	26.7 ± 3.6	22.2 ± 2.5	20.9 ± 2.5
Body weight gain, days 7-14	33.9 ± 5.8	33.7 ± 2.6	18.2 ± 2.5	14.5 ± 2.2
Body weight gain, days 0-14**	75.2	60.4	40.4	35.4
Incidence of clinical symptoms during exposure (%)*				
Decreased breathing rate	3 (60)	2 (40)	5 (100)	5 (100)
Laboured breathing	-	5 (100)	-	5 (100)
Incidence of gross pathological findings in the lung (%)				
Lungs: grey discoloured	1 (20)	3 (60)	1 (20)	1 (20)
Red discoloured spot (one lobe)	1 (20)	-	-	-
Petechia, one lobe	-	-	1 (20)	-

* no clinical symptoms were noted during the post-exposure observation period, ** sum of body weight gain of days 0-7 and 7-14

Another single-dose study on acute inhalation toxicity is available (WIL, 2010) for which the reliability was not further assessed by the eMSCA: According to the study summary, no mortality or any other test item-related toxicity were observed in this study. Apparently only one polyhaloalkene concentration (19 700 ppm nominal) was tested. The reported results are not in disagreement with the findings from (TNO, 2006a) in which the tested concentrations were an order of magnitude higher.

Following 4 h exposure of mice to polyhaloalkene at concentrations of 20000 and 100000 ppm, again no mortality occurred (Huntingdon, 2004). As in the rat study, during the second half of the exposure period, laboured breathing was noted already in the lower dose groups. One of the two males in the low and both males in the high dose group displayed anogenital staining from day 5 (low dose) or day 4 (high dose).

At the end of the 7 d post-exposure period, all animals either had only gained very little or even had lost weight relative to day 0. These observations did not follow a dose-related pattern. Again, a potential influence of polyhaloalkene on body weight gain and terminal body weight of the low dose groups cannot be assessed due to the absence of a negative control group.

This study only served as a range-finding study and therefore only included 2 animals per dose group. An overview of its findings is given in

Table .

Table 17

OVERVIEW OF THE FINDINGS IN THE ACUTE 4 H INHALATION SCREENING STUDY WITH POLYHALOALKENE IN MICE (HUNTINGDON, 2004)		
Sex	**Males (2/group)**	**Females (2/group)**

Dose level (ppm)	20000	100000	20000	100000
Body weight data				
Mean body weight change in g, days 0-7 (individual values)	-0.8 (-2.1/0.6)	-0.3 (0.5/-1.0)	0.1 (0.1/0.1)	-0.6 (-1/-0.2)
Incidence of clinical symptoms during exposure (%)				
Laboured breathing	2 (50)	4 (100)		
Yellow anogenital staining	1 (50)	-	2 (100)	-

The third study, performed in rabbits (Huntingdon, 2011), had a slightly different focus than the studies in mice and rats. In the main phase of this study (designated 'Phase 2'), animals (males, non-pregnant females, and females presumed pregnant) were exposed to concentrations of up to 100000 ppm for 1 h. Again, no mortality occurred. Also, no clinical signs or adverse effects on body weight, macroscopic or microscopic pathology were observed. Thus, no difference in sensitivity or vulnerability of pregnant vs. non-pregnant female rabbits towards acute, 1 h exposure to polyhaloalkene was established.

7.9.2.3. Acute toxicity: dermal

As the evaluated substance is a gas at room temperature and ambient pressure, no studies with dermal administration are available.

7.9.2.4. Acute toxicity: other routes

As the evaluated substance is a gas at room temperature and ambient pressure, no studies with administration via routes other than inhalation are available.

7.9.2.5. Summary and discussion of acute toxicity

Based on the absence of mortality in the available acute inhalation studies in rats, mice, and rabbits, polyhaloalkene does not fulfil the criteria for classification and labelling for acute toxicity as laid down in Reg. (EC) 1272/2008 (CLP).

In the studies with 4 h exposure (i.e. the studies in rats and mice), effects on body weight (development) as well as clinical signs (at and above 20000/200000 ppm in mice/rats, but only when exposure exceeded 2 h) were noted. In addition, pathological findings in the lungs were observed in the rat study.

In contrast, no such symptoms were noted when rabbits were exposed to up to 100000 ppm polyhaloalkene for 1 h.

As a result, LOAECs for (non-lethal) acute toxicity of 20000 ppm or 200000 ppm were derived from the 4 h studies in mice and rats, whereas a NOAEC of 100000 ppm was established for a 1 h exposure in rabbits.

In the view of the eMSCA, the relevance of the results of the mouse study for further risk assessment is low because only two animals per group were tested, there were no macroscopic pathological findings, and no clinical symptoms were reported following exposure to up to 200000 ppm polyhaloalkene in the *in vivo* micronucleus test in mice (cf. section 7.9.6.1.2).

7.9.3. Irritation/corrosion

7.9.3.1. Skin

No studies on skin irritation/corrosion are available as the substance is a gas at room temperature and ambient pressure.

7.9.3.2. Eye

No studies on eye irritation/severe eye damage are available as the substance is a gas at room temperature and ambient pressure. In addition, it was correctly noted by the registrant that no signs of eye irritation were observed in the acute inhalation experiments performed with polyhaloalkene (cf. section 7.9.2.2 above).

7.9.3.3. Respiratory tract

No specific studies on respiratory irritation/corrosion are available. The available database of inhalation studies, many of which include macroscopic and microscopic pathology investigations also of (parts of) the respiratory tract, did not reveal a potential of polyhaloalkene to cause respiratory irritation.

7.9.3.4. Summary and discussion of irritation/corrosion

No specific studies on skin or eye irritation/corrosion have been performed due to polyhaloalkene being a gas at room temperature and ambient pressure. Also no specific study on respiratory tract irritation/corrosion was available for evaluation. When looking at the complete toxicological data base available for polyhaloalkene, there were no indications for an irritant/corrosive potential of polyhaloalkene on skin, eyes, or respiratory tract.

7.9.4. Sensitisation

7.9.4.1. Skin

A skin sensitisation test was not performed, as the registered substance is a gas at room temperature and ambient pressure.

7.9.4.2. Respiratory system

No data on respiratory sensitisation are available. There is currently no accepted and validated test system available for this endpoint. In none of the inhalation tests with repeated administration that have been performed in rats and rabbits, specific indications for a sensitising potential of polyhaloalkene were observed.

7.9.4.3. Summary and discussion of sensitisation

No studies on the sensitising potential of polyhaloalkene are available and there are currently no indications that polyhaoalkene needs to be classified as a skin and/or respiratory sensitiser according to the criteria of the CLP regulation.

7.9.5. Repeated dose toxicity

7.9.5.1. Non-human information

7.9.5.2. Repeated dose toxicity: oral

No repeat-dose studies with oral administration are available due to the registered substance being a gas at room temperature and ambient pressure.

7.9.5.3. Repeated dose toxicity: inhalation

Table 6 (next page) lists the studies on repeated dose toxicity available for polyhaloalkene.

7.9.5.3.1. Minipigs

Göttingen minipigs were exposed to polyhaloalkene concentrations of 0, 5500, and 10000 ppm by whole-body inhalation for 6 h/d, 7 d/wk over a period of two weeks. No adverse effects were noted at the highest dose tested (cf. Table 6). Treatment groups, however, only comprised 2-3 animals per dose level and sex and only two treatment levels were used. The NOAEC of 10000 ppm was confirmed in a follow-up study, in which 8 animals per sex and dose level were exposed to almost the same concentrations (0, 5000, and 10 000 ppm) for 6 h/d, 7 d/wk over a period of four weeks (Huntingdon, 2014).

7.9.5.3.2. Rabbits

Male and female New Zealand White rabbits were exposed to concentrations between 0 and 5500 ppm polyhaloalkene ("HFO-1234yf") for 6 h/d, 7 d/wk, over a period of four weeks (for details cf. Table 6 below) (Huntingdon, 2013b).

Table 6

OVERVIEW OF AVAILABLE REPEAT-DOSE INHALATION TOXICITY STUDIES WITH POLYHALOALKENE					
Method/guideline	**Species, strain, sex, no/group**	**Dose levels (ppm); exposure scheme**	**Results, NOAEC (ppm)**	**Remarks**	**Reference**
Minipigs					
14-day study/similar to OECD 412; reliability: 2 (reliable with restrictions): Only summary available	Pig, Göttingen minipig, M/F, groups 1 and 3: 3 M/3F, group 2: 3 M/2 F	0 - 5500 - 10000; 6 h/d, 7 d/wk, 2 wk	No adverse effects on clinical signs, body weight gain, food consumption, food conversion efficiency, haematology, clinical chemistry, macroscopic and microscopic pathology, no cardiotoxicity **NOAEC:** ≥10000	None	(Huntingdon, 2013a)
28-day study/similar to OECD 412; reliability: 2 (reliable with restrictions): Only summary available	Pig, Göttingen minipig, M/F, 8 per dose level and sex	0 - 5000 - 10000; 6 h/d, 7 d/wk, 4 wk			(Huntingdon, 2014)
Rabbits					
28-day study/OECD 412; GLP*; reliability: 1 (reliable without restrictions)	Rabbit, NZW, M/F, 5/5 (phase 1 controls, 7 d, 14 d interim sacrifice groups, and post-treatment recovery groups) or 10/10 (phase 2 28 d exposure and controls)	Phase 1: a) 7 d sacrifice groups: 0 – 500 - 1 500; 6 h/d, 7 d or 5 500; 6 h/d, 6 d b) 14 d sacrifice groups: 0 – 500 - 1 500 – 4 500; 6 h/d, 7 d/wk, 2 wk Phase 2 (main study): 0 – 500 - 1 000 – 4 500; 6 h/d, 7 d/wk, 4 wk	Mortality: 1 F at 4500 ppm, 1 M/1 F at 5500 ppm Cardiac inflammation: M: ≥1000 ppm; F: ≥ 1500 ppm Skeletal muscle necrosis (minimal to moderate): M/F: ≥ 1500 ppm Clinical chemistry: M:≥1000 ppm; F: ≥500 ppm **NOEC:** < 500 **NOAEC:** 500	None	(Huntingdon, 2013b)

OVERVIEW OF AVAILABLE REPEAT-DOSE INHALATION TOXICITY STUDIES WITH POLYHALOALKENE					
Method/guideline	**Species, strain, sex, no/group**	**Dose levels (ppm); exposure scheme**	**Results, NOAEC (ppm)**	**Remarks**	**Reference**
Rats					
14-day study/OECD 412; GLP; reliability: 1 (reliable without restriction)	Rat, Sprague-Dawley, M/F, 5	0 - 5000 - 20000 - 50000; 6h/d, 5 d/wk, for 2 wk	No adverse effects on clinical signs, body weight gain, food consumption, food conversion efficiency, haematology, clinical chemistry, macroscopic and microscopic pathology **NOAEC**: ≥50 000	None	(TNO, 2005d)
28-day study/OECD 412+ (combined repeat-dose inhalation study, Unscheduled DNA Synthesis Test, and Micronucleus Test); GLP; reliability (RDT part): 1 (reliable without restriction)		0 - 5000 - 15000 - 50000; 6h/d, 5 d/wk, for 4 wk, followed by a 14 d recovery period		For results of the *in vivo* genotoxicity tests, cf. section 7.9.6.1.2	(TNO, 2006b)
28-d study/OECD 412; GLP*; reliability 4 (not assignable)$	Rat, Crl:CD(SD), M/F, 5	0 – 200 – 400 - 800; 6 h/d, 5 d/wk, for 4 wk	No adverse effects on clinical signs, body weight gain, food consumption, food conversion efficiency, haematology, clinical chemistry, macroscopic and microscopic pathology **NOAEC**: ≥800	Only 5 animals/group	Unknown, 2010$
90-day study/OECD 413; GLP; reliability 1 (reliable without restriction)	Rat, Sprague-Dawley, M/F, 10	0 - 5000 - 15000 - 50000; 6 h/d, 5 d/wk, for 14 wk (64-65 exposure days)	No adverse effects on clinical signs, body weight gain, food consumption, food conversion efficiency, haematology, clinical chemistry, macroscopic and microscopic pathology **NOAEC**: ≥50 000	None	(TNO, 2009)

* Claimed but no certificate available for this evaluation; $ The test is summarised on ECHA's dissemination site as being part of an opt-out registration dossier which, however, is no longer available in the ECHA MSCA IUCLID database. No bibliographic information about this reference is available, and hence, its reliability cannot be assessed.

Since the eMSCA only had access to the registrant's summary of the study (which is now available via ECHA's dissemination site), below the summary by the German MAK Commission is cited[9], which was based on the full study report:

*"Groups of 25 male and 25 female rabbits were exposed to 2,3,3,3-tetrafluoropropene concentrations of 0, 500, 1500/1000 or 5500/4500 ppm in whole animal exposure chambers for 6 hours a day, for 28 days. Five animals per sex and group were sacrificed on days 8 and 15, 10 animals per sex and group were sacrificed on day 29 after the beginning of exposure and 5 animals were observed for 28 days. Because of the increase in the total creatine kinase activity and the histopathological changes in the heart muscle after exposure for 7 and 14 days, the concentration in the group exposed to 1500 ppm was lowered from 1500 to 1000 ppm in the last 2 weeks. As 2 animals of the group exposed to 5500 ppm had not survived after the first 7 exposure days, the animals were subsequently exposed only on 6 days per week instead of 7 days. The cause of death of the 2 animals is unclear. On day 8, the concentration of 5500 ppm was reduced to 4500 ppm (***Error! Not a valid bookmark self-reference.***).*

Table 7

EXPOSURE PATTERN OF THE 28-D INHALATION STUDY WITH POLYHALOALKENE IN RABBITS, ((HUNTINGDON, 2013B), ADAPTED FROM (MAK COMMISSION, 2015))						
Group	**Exposure (ppm)**	**No. animals (M/F)**	**Interim sacrifices M/F**			**Recovery period (28 d)**
			Day 8	**Day 15**	**Day 29**	
1	0	25/25	5/5	5/5	10/10	5/5
2	500	25/25	5/5	5/5	10/10	5/5
3	1 500/1 000	25/25	5/5	5/5	10/10	5/5
4	5 500/4 500	25/25	4/4	5/4	10/9	5/5

*[...] Clinical symptoms were not observed, nor were there any changes in body weights or feed consumption. Likewise, blood values, coagulation, blood gases and urinary values were unaffected. On day 8 of exposure, the relative liver weights were significantly increased in male rabbits. After 28 days recovery, the liver weights were again in the range of those of the control animals. At 1000 ppm and above, both the females and males of the interim sacrifice groups were found to have subacute/chronic myocardial inflammation that was characterized by small lymphocyte aggregates, macrophages and neutrophilic granulocytes and associated with foci of degeneration and necrosis. Degeneration and necrosis were considered to be a result of the inflammatory process rather than a separate finding. The incidence and severity of the findings did not increase with the exposure period (*Table 8*).*

Table 8

INCIDENCES OF MYOCARDIAL INFLAMMATION AND SKELETAL MUSCLE NECROSIS IN RABBITS AFTER EXPOSURE TO POLYHALOALKENE BY INHALATION (REPRODUCED FROM (MAK COMMISSION, 2015))								
Dose level (ppm)	**0**		**500**		**1 500/1 000**		**5 500/4 500**	
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Myocardial inflammation								
Day 8	0/5	0/3	0/5	0/3	1/5	0/5	5/5	2/6
Day 15	0/5	0/5	0/5	0/5	0/5	2/5	2/5	0/4
Day 29	0/10	0/10	0/10	0/10	1/10	0/10	6/10	4/10
Recovery	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
Skeletal muscle necrosis								
Day 8	3/5	3/5	3/5	2/5	3/5	2/5	0/4	0/5
Day 15	2/5	1/5	2/5	2/5	4/5	4/5	3/5	2/4
Day 29	3/10	3/10	2/10	2/10	3/10	3/10	5/10	6/10
Recovery	1/5	3/5	3/5	5/5	0/5	0/5	1/5	3/5

[9] Adapted typographically to this document, also adapted with respect to table numbers and „mL/m³" replaced by „ppm".

After 28 days recovery, myocardial inflammation to 2,3,3,3-tetrafluoropropene was no longer observed in any rabbit. As necrosis was detected histopathologically during treatment, the finding is considered to be a sign of persistent defect after healing.

*Acute skeletal muscle necrosis was found in control group animals and exposed animals at all times of exposure and irrespective of sex. It was characterized by myofibrillar loss, hyaline degeneration in the sarcoplasm and the loss of transverse striation. Signs of inflammation, fibrosis or the transformation of myofibrils to adipose tissue were not observed. There was no concentration-related increase in the incidence or severity of muscular necrosis (Table 8). After 28 days recovery, the incidence and severity of muscular necrosis in the exposed rabbits was similar to that in the control animals. Unlike rats and mice, rabbits react very sensitively to a diet that is not balanced exactly as regards vitamin E and selenium. This may be the case especially during pregnancy. Therefore, small (multi)focal foci of necrosis or histiocytic reactions may often be observed in both heart and skeletal muscles. Moreover, intermediate stages of parasitic diseases are more common in the muscles of rabbits. For all these reasons, muscular findings are not unusual in rabbits. The total creatine kinase activity in female and male rabbits was significantly increased on day 29 at 1000 ppm and above. This effect was observed in females as early as after 8 days of exposure. In male rabbits, the total creatine kinase activity was increased even at 500 ppm after 28 days recovery. However, this increase was not related to the concentration. As the creatine kinase activity in the group exposed to 500 ppm was not increased at any other time of investigation, a NOAEC of 500 ppm was derived from this study (*Table 9*). As the concentration in the 2 higher exposure groups was reduced during the study, it is difficult to assess whether the effects increased with the exposure period. In the middle concentration group, the prevalence of myocardial inflammation increased in both sexes from 10% to 20% in the period from days 8 to 15; subsequently, after the concentration had been lowered to 1000 ppm, the prevalence was 5%. The same applies to skeletal muscle necrosis; its prevalence was no longer increased after the concentration was lowered to 1000 ppm. This is evidence that the exposure period has less influence than the concentration, at least at concentrations in the range of the NOAEC. However, the prevalence of myocardial inflammation in the animals of the high concentration group increased from 20% to 50% from day 15 to day 29. Therefore, after prolonged exposure, the severity can be expected to increase markedly at concentrations that cause effects."* (MAK Commission, 2015)

Table 9

CLINICO-CHEMICAL EFFECTS IN RABBITS AFTER EXPOSURE TO POLYHALOALKENE BY INHALATION((HUNTINGDON, 2013B), ADAPTED FROM (MAK COMMISSION, 2015))		
Day of examination	**Dose level (ppm), sex**	**Findings (in blood)**
Day 8	500, M/F	No clinico-chemical effects
	1 500, M	Total protein ↓; albumin ↓
	1000, F	Creatine kinase MM ↑; fatty acid binding protein ↑
	5500, M	Alanine aminotransferase ↑; urea ↑; total creatine kinase ↑; creatine kinase MM ↑; myoglobin ↑
	5500, F	Total creatine kinase ↑; creatine kinase MM ↑; alanine aminotransferase ↑; fatty acid binding protein↑; myoglobin ↑
Day 15	500, M/F	No clinico-chemical effects
	1500, F	Total creatine kinase ↑; myoglobin ↑; creatine kinase MM ↑
	4500, M	Total creatine kinase ↑; Ca^{2+} ↓; creatine kinase MM ↑; myoglobin ↑
	4500, F	Aspartate aminotransferase ↑; prothrombin time ↓; total creatine kinase ↑; creatine kinase-MB ↑
Day 29	500, M/F	No clinico-chemical effects
	≥ 1000, M	Total creatine kinase ↑; Ca^{2+} ↓; creatine kinase MB ↑
	≥ 1000, F	Total creatine kinase ↑; creatine kinase MM ↑; fatty acid binding protein↑; myoglobin ↑
	4500, M	Creatine kinase MM ↑; fatty acid binding protein ↑
	4500, F	Aspartate aminotransferase ↑; alkaline phosphatase,

		glucose ↑
Recovery period	≥ 500, M	Total creatine kinase increased but not in a concentration-dependent manner↑; phosphate ↑

Creatine kinase MM: Skeletal muscle; creatine kinase MB: heart

In an expert statement provided for the registrants, the relevance of cardiac findings in rabbits for humans is questioned. The statement points out that (mini)pigs were a more suitable model for human cardiac toxicity than rabbits, given their *"comparable coronary anatomy, comparable electrophysiological functions and major ion channels, and comparable reactions to harmful influences. […] the rabbit is not considered a suitable animal model because of the critical structural, functional, and molecular differences between rabbit hearts and larger mammalian hearts (e.g., pigs and humans). Importantly, rabbits have a high prevailing sympathetic tone, whereas humans and pigs have a prevailing vagal tone. The higher sympathetic tone of the rabbits predisposes them to atrial and ventricular arrhythmias and limits extrapolation of findings in rabbits to humans"* (Feldman and Mann, 2013). However, this statement fails to provide a convincing link between the claimed differences between rabbits and humans and the myocardial inflammation seen after exposure of rabbits to polyhaloalkene. As a consequence, relevance of these effects for humans cannot be ruled out and therefore the eMSCA agrees with (MAK Commission, 2015) in that the NOAEC of 500 ppm in rabbits as the most sensitive species should be used as the Point of Departure (PoD) for further risk assessment.

7.9.5.3.3. Rats

A total of three assessable repeat-dose toxicity studies with polyhaloalkene in SD rats is available, using dose levels of up to 50 000 ppm and covering exposure periods of 14, 28, and 90 d, respectively (TNO, 2005d; TNO, 2006b; TNO, 2009). In none of these studies, adverse effects were reported at any dose level.

The ECHA dissemination site lists a further study in SD rats. Since the entry on the dissemination site neither contains any bibliographic information nor discloses the identity of the respective registrant, its reliability could not be assessed by the eMSCA. According to the summary on the dissemination site, no mortality or any other test item-related toxicity were observed in this study. Apparently only one polyhaloalkene concentration (19700 ppm nominal) was tested and therefore the reported results are not in disagreement with the findings from (TNO, 2006a) in which the tested concentrations were higher by an order of magnitude.

No relevant treatment-related findings were noted in any of the above studies. 50000 ppm is the NOAEC for repeat-dose toxicity of polyhaloalkene in rats. This is also in line with the NOAEC of 50000 ppm for maternal toxicity from the study on pre-natal development toxicity in (Wistar) rats (cf. section 7.9.7.5.1).

7.9.5.3.4. Repeated dose toxicity: Dermal

No repeat-dose studies with dermal administration are available due to the registered substance being a gas at room temperature and ambient pressure.

7.9.5.3.5. Repeated dose toxicity: Other routes

Only repeat-dose studies with administration via inhalation are available due to the registered substance being a gas at room temperature and ambient pressure.

7.9.5.4. Human information

No human data on the toxicity of polyhaloalkene after repeated administration are available.

7.9.5.5. Summary and discussion of repeated dose toxicity

No relevant effects were observed in studies with repeated administration of polyhaloalkene to rats by inhalation for 2, 4, and 13 weeks, respectively. For this species, the NOAEC for repeated dose toxicity (up to 90 d) is 50000 ppm, the highest dose tested. Rabbits were much more sensitive to repeated administration of polyhaloalkene: In a 28 d repeated dose toxicity study, the NOAEC was 500 ppm, based on cardiac inflammation and skeletal muscle necrosis, accompanied by clinical chemistry changes which, however, were not noted in satellite recovery group 28 d after the end of exposure.

Based on these results, polyhaloalkene does not fulfil the criteria for classification and labelling with respect to Specific Target Organ Toxicity (STOT) as defined by Regulation (EC) 1272/2008.

7.9.6. Mutagenicity

7.9.6.1. Non-human information

The available studies on mutagenicity are summarised in Table 10 and Table 11.

7.9.6.1.1. *In vitro* data

In a bacterial reverse mutation assay (TNO, 2005a) using a gas exposure chamber, polyhaloalkene was mutagenic in the *S. typh.* TA100 and *E.coli* WP2 u□rA strains in the presence, but not in the absence of S9 mix .

A chromosomal aberration test exposing cultured human lymphocytes (TNO, 2005b) to the test substance using a modular incubator chamber gave a negative test result.

The ECHA dissemination site lists a further bacterial reverse mutation test and a further chromosomal aberration test, both apparently from 2009 and submitted with an opt-out dossier, which are not present in the MSCA IUCLID registration database (as of 26 September 2018). Since the entries on the dissemination site neither contain any bibliographic information nor disclose the identity of the respective registrant, their reliability could not be assessed by the eMSCA. According to the summaries on the dissemination site, both tests were negative ± S9, however the maximum concentrations tested were lower than those used in the two corresponding tests for which more deailed information is available, i.e. (TNO, 2005a; TNO, 2005b).

In an in vitro mammalian cell gene mutation test, cultured mouse lymphoma L5178Y cells were incubated with polyhaloalkene concentrations ≤ 760000 ppm. The test was positive at concentrations ≥ 200 000 ppm, but only in the presence of S9 mix (TNO, 2015b).

7.9.6.1.2. *In vivo* data

Three *in vivo* micronucleus (MN) tests in mammalian erythrocytes are available:

- an experiment with a single, acute 4 h-exposure of CD-1 mice to polyhaloalkene with administration of up to 200000 ppm (TNO, 2005c);
- a test from 2010 in which rats were treated with analytical concentrations of up to 1700 ppm polyhaloalkene; this test is listed on ECHA's dissemination site as part of an opt-out dossier, but it is not present in the MSCA IUCLID registration database (as of 26 September 2018). Since the entry on the dissemination site neither contains any bibliographic information nor discloses the identity of the respective registrant, its reliability could not be assessed by the eMSCA. Nevertheless, even without sufficient knowledge about the details of this experiment it is evident that the concentrations applied were too low and therefore the negative result obtained is not sufficiently reliable; and
- a subacute study with administration of up to 50000 ppm polyhaloalkene over a period of 28 d (TNO, 2006b).

Table 10

OVERVIEW OF *IN VITRO* GENOTOXICITY STUDIES AVAILABLE FOR POLYHALOALKENE					
Method/guideline	**Test system**	**Test concentrations (ppm); metabolic competence; incubation time**	**Results**	**Remarks**	**Reference**
Bacterial reverse mutation test (Ames test)/OECD 471; GLP; reliability: 1 (reliable without restrictions)	S. typh. TA 98, TA 100, TA 1535, TA1537; E.coli WP2 u□rA	100000 – 200000 – 400000 – 600000 - 760000; ± S9; 4 h (± 15 min)	TA100 and E.coli: Positive +S9 (mutagenic); Slightly toxic to TA100 (-S9); All other strains: No significant difference in number of revertants (non-mutagenic)	None	(TNO, 2005a)
Bacterial reverse mutation test (Ames test)/OECD 471; GLP*; reliability: 4 (not assignable)$		15000 – 30000 – 60000 – 90000 – 120000; ±S9; 48 h	Negative ±S9; no cytotoxicity	In a range-finding study, a higher test concentration of 500000 ppm was employed and a positive result was obtained. Test concentrations too low	Unknown$, 2009
Chromosomal aberration test/OECD 473; GLP; reliability: 1 (reliable without restrictions)	Cultured human lymphocytes from peripheral blood	100000 - 200000-400000 - 600000-760000; ± S9; 1 x 4 h	Negative for chromosomal aberrations (not clastogenic); Slight cytotoxicity (-S9) after 48 h at 760000 ppm	None	(TNO, 2005b)
Chromosomal aberration test/OECD 473; GLP*; reliability: 4 (not assignable)$		7500 – 15000 – 30000 – 60000 – 90000 – 120000; ± S9; 1 x 4 or 1 x 24 h	Negative for chromosomal aberrations (not clastogenic)	None	Unknown, 2009$
In vitro mammalian cell gene mutation test/OECD 476; GLP*; reliability: 2 (reliable with restrictions, only summary available to the eMSCA)	Cultured mouse lymphoma L5178Y cells	100000 - 200000 - 400000 - 600000-760000; ± S9; 1 x 4 h	-S9: negative; +S9: positive ≥ 200000 ppm	None	(TNO, 2015b)

* Claimed but no certificate available for this evaluation; $ The test is summarised on ECHA's dissemination site as being part of an opt-out registration dossier. No bibliographic information about this reference is available, and hence, its reliability cannot be assessed.

Table 11

OVERVIEW OF AVAILABLE *IN VIVO* INHALATION GENOTOXICITY STUDIES WITH POLYHALOALKENE					
Method/guideline	**Species, strain, sex, no/group**	**Dose levels (ppm), exposure scheme**	**Results**	**Remarks**	**Reference**
Mammalian erythrocyte micronucleus test/OECD 474; GLP; reliability: 2 (reliable with restrictions)	Mouse, CD-1 SPF, M, 5 (low and mid dose, positive control) or 10 (negative control, high dose)	0 - 12500 - 50000 – 200000; 1 x 4 h	Negative; no clinical signs observed	No cytotoxicity was demonstrated	(TNO, 2005c)
Mammalian erythrocyte micronucleus test/OECD 474; GLP*; reliability: 4 (not assignable)$	Rat, Sprague-Dawley, M/F, 5	0 – 425 - 850 – 1700; 3 x 6 h/d	Negative; no clinical signs, effects on survival, body weight, and food consumption	No cytotoxicity was demonstrated	Unknown$, 2010
Combined repeat-dose inhalation study, UDS and Micronucleus Test, Micronucleus module/OECD 474; GLP; reliability: 1 (reliable without restrictions)		0 – 5000 -15000 - 50000; 6 h/d, 5 d/wk, for 28 d; Mitomycin C was applied as positive control via i.p. injection (20 mL/kg bw; 2.5 mg/mL in corn oil)	Negative response for negative control and groups treated with polyhaloalkene, positive response for positive control	For results of the repeat-dose toxicity module, cf. section 5.6.1.2	(TNO, 2006b)
Combined repeat-dose inhalation study, UDS and Micronucleus Test, UDS module/OECD 486; GLP; reliability: 2 (reliable with restrictions)		0 – 1500 - 50 000; 6 h/d, 5 d/wk, for 28 d; 2-AAF was applied as positive control via gavage (20 mL/kg bw; 2.5 mg/mL in corn oil))	Negative response for negative control and groups treated with polyhaloalkene, positive response for positive control	Deviations from OECD 486 (cf. text). For results of the repeat-dose toxicity module, cf. section 5.6.1.2	(TNO, 2006b)
Combined bone marrow micronucleus test and comet assay/ OECD 489; GLP*; reliability: 2 (reliable with restrictions: Only summary available to the eMSCA)	Rat, Wistar, M, 5	0 – 5000 – 15000 – 50000; 2 x 6h + 1 x 2 h on three successive days	Negative for chromosomal damage, damage to the mitotic spindle apparatus in bone marrow cells, and induction of primary DNA damage in liver and lung cells; Positive controls: MMC, MMS, 2-AAF	None	(TNO, 2015a)

* Claimed but no certificate available for this evaluation; $ The test is summarised on ECHA's dissemination site as being part of an opt-out registration dossier. No bibliographic information about this reference is available, and hence, its reliability cannot be assessed.

The latter test was performed in satellite groups within the 28-d repeat-dose toxicity test already summarised above (section 7.9.5.3). Moreover, in the same study, further satellite groups were used to carry out an Unscheduled DNA Synthesis Test (UDS test).

While both MN tests complied with guideline requirements (including confirmation of systemic bioavailability and application of sufficiently high test concentrations) and yielded reliable negative results, the UDS test was found to deviate substantially from the corresponding OECD test guideline which compromised its validity. As a consequence, the eMSCA concludes that this study is not suitable to prove the absence of mutagenicity in rats *in vivo.* Specifically, the critical deviation identified was the time of tissue sampling.

The endpoint (UDS) measured is indicative of DNA damage and subsequent repair in liver cells. The increase in the rate of DNA repair can be measured in isolated, cultured cells from the target tissue after introducing radioactively labelled DNA building blocks (such as [methyl-^{3}H]-thymidine) into the culture medium. However this enhanced repair activity will only be detectable during a certain time window. After the mutagen has been cleared from the target tissue, the rate of DNA repair will eventually return to normal. As a consequence, if sampling of the cells occurs too late, mutagenic activity might be missed. For this reason, the corresponding OECD test guideline specifies the following procedure:

'[…] Liver cells are prepared from treated animals normally 12-16 hours after dosing. An additional earlier sampling time (normally 2-4 hours post-treatment) is generally necessary unless there is a clear positive response at 12-16 hours. However, alternative sampling times may be used when justified on the basis of toxicokinetic data.'

In contrast, while the study authors sampled cells from animals treated with positive controls 12-16 h after exposure, samples from the polyhaloalkene treatment groups apparently were only taken once 'within 24 hours after the last exposure period'. No scientific justification (as demanded by the OECD test guideline) for this deviation was provided. Based on the available toxicokinetic data the eMSCA considers a justification as not possible.

In addition, a combined *in vivo* bone marrow micronucleus test and comet assay in which Wistar rats were exposed to polyhaloalkene concentrations of ≤ 50 000 ppm for 2 x 6 h and 1 x 2 h on three successive days has become available to the eMSCA as the result of an information request issued in the course of this SEv. The registrants in their summary (as available on the ECHA dissemination site) concluded that under the conditions of this test polyhaloalkene did not induce chromosomal damage, did not damage the mitotic spindle apparatus in bone marrow cells, and did not induce primary DNA damage in liver and lung cells of the exposed rats (TNO, 2015a).

7.9.6.2. Human information

No information on a mutagenic potential of polyhaloalkene in humans is available.

7.9.6.3. Summary and discussion of mutagenicity

Polyhaloalkene showed mutagenicity in bacterial and mammalian cells *in vitro* (TNO, 2005a; TNO, 2015b), but only in the presence of S9 mix. However, based on the results of an UDS test, albeit of limited reliability (TNO, 2006b), and a comet assay (TNO, 2015a), this effect was not confirmed *in vivo*. Based on the complete available database on mutagenicity it is concluded that polyhaloalkene does not need to be classified/labelled for mutagenicity.

7.9.7. Carcinogenicity

7.9.7.1. Non-human information

7.9.7.1.1. Carcinogenicity: oral

As polyhaloalkene is a gas at room temperature and ambient pressure, no carcinogenicity studies in animals with oral administration are available.

7.9.7.1.2. Carcinogenicity: inhalation

No conventional carcinogenicity study in animals with administration via inhalation is available for polyhaloalkene (cf. Table 12).

A toxicogenomics study has been submitted in order to gain deeper insight into the potential of polyhaloalkene to act as a carcinogen (Hamner Institute, 2008). Polyhaloalkene was administered via whole-body inhalation to groups of 10-12 female B6C3F1 mice and male F344 rats for a period of 90 days at concentrations of 0, 10000, and 50000 ppm.

In parallel, other groups were exposed to varying dose levels and via different routes of assumed carcinogens and non-carcinogens, including corresponding vehicle controls. Assumptions on the carcinogenic potential of these chemicals were based on previous evaluations under the umbrella of the US National Toxicology Program (NTP). Data for four additional chemicals were included from previous studies. For an overview, cf. Table 13.

In week 12, samples for later metabonomics analysis were obtained. At the end of the 13-wk exposure, animals were euthanised and tissues removed for further analysis. Genome-wide microarray analysis (using Affymetrix Rat Genome 230 and Mouse Genome 430 arrays) and histopathological evaluation were performed on the mouse liver and rat kidney tissues.

Additional gene expression data for two mouse liver carcinogens and two non-carcinogens were used from an earlier study. The gene expression data were analysed using statistical classification models to identify potential short-term gene expression biomarkers that were predictive of a chemically-induced increase in mouse liver and/or rat kidney tumour incidence. The biomarkers were then used to predict the carcinogenic potential of polyhaloalkene.

Based on the observed gene expression changes in the male rat kidney following exposure to the positive and negative control chemicals, a statistical classification model was constructed. Different numbers of genes were evaluated in a feature selection process to assess the change with gene number in predictive accuracy. Peak accuracy in predicting rat kidney tumours was obtained with only 5 genes, but the model showed a lower predictive accuracy than had been previously observed in an experiment in the mouse lung (Hamner Institute, 2008).

Table 12

OVERVIEW OF AVAILABLE CARCINOGENICITY DATA FOR POLYHALOALKENE						
Method/ guideline	**Route**	**Species, strain, sex, no/group**	**Dose levels (ppm); exposure scheme**	**Results**	**Remarks**	**Reference**
Toxicogenomics assess-ment of carcinogenic potential/no specific guideline available; Non-GLP	Inhalation, whole body; for model carcinogens and non-carcinogens, also dosing via gavage or feeding was chosen	Mouse, B6C3F1/ Crl, F, 10-12; Rat, F344/ CrlBR, M, 10-12	0 – 10000 - 50000; 6 h/d, 5 d/wk, for 13 wk For comparative analysis: Positive and negative controls (see text for details)	According to the study authors, the models obtained predicted non-carcinogenicity of polyhaloalkene both in female mouse liver and male rat kidney. Evidence of gene expression changes in rat kidney associated with endocrine effects (reduction in circulating androgens) and hypertension. In the view of the German CA, the results from this test cannot be used to draw conclusions on the carcinogenic potential or on any other potential toxic effects of polyhaloalkene (cf. text for details)	Exposure concentration of polyhaloalkene varied considerably over time	(Hamner Institute, 2008).

Table 13

OVERVIEW OF THE TEST SUBSTANCES USED IN THE TOXICOGENOMICS STUDY (HAMNER INSTITUTE, 2008)					
Substance	**Route**	**Vehicle**	**Dose levels; exposure scheme**		**Remarks**
			Rat	**Mouse**	
Substances tested					
Tetrafluoroethylene (TFEL)	Inhalation	Air	625 ppm; 6 h/d, 5 d/wk	1250 ppm; 6 h/d, 5 d/wk	Assumed carcinogenic
1-Amino-2,4-dibromoanthraquinone	Oral, diet	Feed	10 g/kg feed; 7 d/wk	20 g/kg feed; 7 d/wk	
Tris(2,3-dibromopropyl) phosphate	Oral, diet	Feed	100 mg/kg feed; 7 d/wk	1 g/kg feed; 7 d/wk	
Trichlorofluoromethane	Oral, gavage	Corn oil	977 mg/kg bw/d; 5 d/wk	3925 mg/kg bw/d	Assumed non-carcino-genic
Tetrafluoroethane (TFEA)	Inhalation	Air	50000 ppm; 6 h/d, 5 d/wk	50000 ppm; 6 h/d, 5 d/wk	
Iodoform	Oral, gavage	Corn oil	142 mg/kg bw/d; 5 d/wk	93 mg/kg bw/d; 5 d/wk	
N-(1-naphthyl)ethyl-enediamine dihydro-chloride	Oral, diet	Feed	1 g/kg feed; 7 d/wk	-	
Results used from previous studies (mouse liver carcinogenicity only)					
1,5-Naphthalenediamine					Assumed carcinogenic
Benzofuran					
N-(1-naphthyl) ethylenediamine dihydrochloride					Assumed non-carcinogenic
Pentachloronitrobenzene					

The sensitivity was generally poor with the ability to detect only 73.3% of the carcinogenic compounds. Tetrafluoroethylene (TFEL), one out of only three positive chemicals in the rat training dataset, was consistently misclassified. One interpretation of the author was that for a presumed weaker carcinogen such as TFEL the current genomic approach with small numbers of positive and negative control chemicals failed to provide a correct prediction. In the view of the eMSCA this would then also compromise the ability of the test to detect a 'weak' carcinogenic effect of polyhaloalkene. Another interpretation was given in a later supplement to the original study report, where the author noted that the original NTP study for TFEL had used a different strain of Fischer rats and that histopathological kidney findings from the NTP study were not reproduced in his own study. As a consequence, the author speculated that in fact the prediction of the model for TFEL might be correct for the strain used here. However, recalculation of the model under the assumption that TFEL was non-carcinogenic apparently was not performed.

In a similar fashion, a statistical classification model was constructed for the classification of mouse liver carcinogenicity. The combined dataset (cf. Table 13 above) represented a total of five chemicals positive for female mouse liver tumours in the NTP rodent bioassay, five chemicals negative for female mouse liver tumours, and three associated vehicle control groups. A peak accuracy of 98.5% was obtained with 50 genes with a sensitivity and specificity of 97.2 and 99.2%, respectively. The peak predictive accuracy, sensitivity,

and specificity were in line with what had been observed previously for mouse lung tumours (Hamner Institute, 2008). This predictive set of 50 genes together with the support vector machine (SVM) model was then used to predict the carcinogenic potential of the test chemical polyhaloalkene. The statistical classification model predicted the two doses of polyhaloalkene to be non-carcinogenic in the female mouse liver. For these 50 genes, the gene expression changes for polyhaloalkene were significantly different from the positive controls and were more similar to the fluorinated negative control TFEA treatment group and the air control group thereby (in the view of the author) supporting a potential classification of polyhaloalkene as non-carcinogenic in the female mouse liver.

Aside from the analysis for carcinogenicity, the study also included a genome-wide search for characteristic, treatment-related changes in gene expression. In the male rat kidney exposed to polyhaloalkene, the expression of 12 genes was significantly changed at the low dose; 21 genes were significantly changed at the high dose. Only three genes (RGD1311126, Cpe, and RGD1310433) were significantly altered at both doses. The author concluded that, as a whole, these gene expression changes in the kidney were *"[…] highly suggestive of endocrine-related effects"* for polyhaloalkene at the applied doses *(Hamner Institute, 2008).*

In particular, the author claimed that, based on the results of a number of third party studies, the following changes in gene expression could be interpreted as signs of a reduction of circulating androgens:

- The organic anion transporter Slc22a7 was significantly increased at the low dose. Its expression was also increased at the high dose, but this increase was not statistically significant.
- Cytochrome P-450 CYP2C (aka CYP2C11) and prostaglandin D2 synthase (Ptgds) were both significantly downregulated at the low dose of polyhaloalkene. Similar to Slc22a7, the expression of CYP2C11 and Ptgds were also altered at the higher dose, but the results were not statistically significant.
- At the high dose, 15-hydroxyprostaglandin dehydrogenase (Hpgd) and ELL associated factor 2 (Eaf2) were significantly upregulated.

In a later supplement to the study report, it was stressed by the study author that the biological significance of these associations could not be judged in isolation and that a two-generation reproductive toxicity study (which was in the planning stage at that time) should further elucidate this point. This later multigeneration study, however, did not show effects on fertility in terms of the reproductive outcome; on the other hand, a delay in vaginal opening was noted (cf. section 7.9.7.4 for details).

Apart from the alleged endocrine effects of polyhaloalkene, treatment at the high dose also upregulated the 'Spontaneously hypertensive rat-clone A hypertension-associated gene' (Sah) and cytochrome p-450 CYP1A1. According to the author, increased expression of Sah has been associated with hypertension in the rat and follow-up studies on the human homologue of this gene had identified a polymorphism that caused increased expression. Apparently, the increase in expression was significantly associated with increases in body mass index, triglyceride levels, cholesterol, and blood pressure status.

As to the biological significance of these findings, hypertension was not specifically assessed in any of the available studies with repeated administration of polyhaloalkene.

In livers of female mice exposed to polyhaloalkene, no genes were significantly changed at the low dose and the expression of only two genes, Akr1b7 and Qrsl1, was significantly changed at the high dose. According to the author, aldo-keto reductase family 1, member B7 (Akr1b7) is an enzyme that reduces isocaproaldehyde produced by cholesterol sidechain cleavage in the first step of steroidogenesis. Reportedly, the gene is primarily expressed in mouse steroidogenic tissues such as the adrenal cortex, testis, and ovary and expression of the gene has been shown to be regulated by testosterone and the pituitary hormone ACTH. Glutaminyl-tRNA synthase (glutamine-hydrolysing)-like 1 (Qrsl1) is a relatively uncharacterised gene and the significance of Qrsl1 upregulation in terms of adverse biological effect is unknown.

7.9.7.1.3. Carcinogenicity: dermal

Due to polyhaloalkene being a gas at room temperature and ambient pressure, no carcinogenicity studies in animals with dermal administration are available for polyhaloalkene.

7.9.7.2. Human information

No carcinogenicity data in humans are available for polyhaloalkene.

7.9.7.3. Summary and discussion of carcinogenicity

Overall, it is difficult to judge the robustness and biological significance of the findings reported in the toxicogenomics experiment (Hamner Institute, 2008). Some of the conclusions appear highly speculative. Based on the following considerations, the eMSCA concludes that the results of this study do not constitute an appropriate basis to conclude on the pre- or absence of a carcinogenic potential for polyhaloalkene:

- The number of model substances used for building the prediction models appears far too small to arrive at a meaningful interpretation of the results. Basic aspects of model validation such as external validation have not been reported. Model and target substance were administered at highly variable dose levels and via various routes. In particular the influence of the latter point on gene expression in liver and kidney has not been discussed.
- The mechanistic basis for the carcinogenic action of the positive model compounds was not reported. Consequently, there is no compelling argument why the substances chosen were assumed to be particularly similar to polyhaloalkene in terms of structure and/or mechanism/mode of action and thus were selected for this study.
- One out of three rat carcinogenicity model compounds was not predicted correctly. The reason for this – according to the study author – was that the substance under question, tetrafluoroethylene (TFEL), was only a 'weak' carcinogen. Notably, in ECHA's Classification & Labelling Inventory (as of October 13, 2018) 178 (including 113 from joint entries) out of 643 notifiers have classified TFEL as Carc. 1B (and another notifier has assigned Carc. 2). Therefore, the sensitivity of the prediction model to detect relevant carcinogens appears questionable.
- Animals were exposed for 90 days only, which introduces additional uncertainty when concluding on lifetime carcinogenicity.
- The investigation was performed in one sex of each species only, therefore sex-dependent expression patterns are not covered.
- Finally, experimental problems were encountered in the course of this study, in particular difficulties in keeping polyhaloalkene exposure levels constant, that further compromise the results. In addition, the study was not performed according to GLP.

In summary, no reliable carcinogenicity data for polyhaloalkene are currently available for experimental animals or for humans. Since polyhaloalkene is not classified as a germ cell mutagen of (at least) CLP category 2 (cf. section 7.9.6.3) and the available repeated dose studies have not resulted in test substance-related neoplastic or pre-neoplastic lesions, there is currently no indication of a carcinogenic potential of polyhaloalkene.Toxicity to reproduction (effects on fertility and developmental toxicity)

7.9.7.4. Effects on fertility

7.9.7.4.1. Non-human information

For polyhaloalkene, a two-generation study in rats is available which is summarised in **Error! Reference source not found.**6 (TNO, 2011).

Table 14

OVERVIEW OF AVAILABLE FERTILITY STUDIES WITH POLYHALOALKENE						
Method/ guideline	**Route**	**Species, strain, sex, no/group**	**Dose levels (ppm); exposure scheme**	**Results**	**Remarks**	**Reference**
Two-generation study/OECD 416; GLP; reliability 2 (reliable with restrictions)	Inhalation, nose-only/whole body (see text for details)	Rat, Wistar Crl:WI(WU), M/F, 28	0 – 5000 – 15000 – 50000	No test substance-related adverse effect on clinical signs or mortality, organ weight, oestrus cycle, reproduction or fertility parameters, pup sex ratio, pup body weight (changes), sperm quality, male onset of puberty ≥ 5000 ppm: Slightly reduced feed consumption and body weight gain vs. control in all treatment groups at various time-points. Increase in pre-coital time (F0), increase in duration of gestation (F0). See text for discussion of adversity and biological relevance. ≥ 15000 ppm: F1: Apparent delay in the onset of puberty (vaginal opening); Increase in pre-coital time (F1), prolonged duration of gestation (F1) 50000 ppm: Number of pups lost during PND 1-4 (F1) **$NOAEC_{maternal}$**: 50000 ppm **$NOAEC_{fertility}$**: 50000 ppm **$NOAEC_{development}$**: 5000	The registrant concluded on a NOAEC of 50000 ppm	(TNO, 2011)

F0 animals were exposed to polyhaloalkene via nose-only inhalation throughout pre-mating (males and females), during mating, and through gestation day (GD) 19 (females). Between GD 0 and 4, treatment was apparently interrupted. From GD 5 until weaning of the F1 pups (day 21 of lactation), polyhaloalkene was administered to F0 females via whole-body inhalation. It is unclear whether this exposure took place in the presence or absence of the pups. F1 animals received polyhaloalkene via whole-body inhalation from weaning until they were about six weeks of age. Afterwards the administration mode returned to nose-only inhalation until termination of the study. Under this scheme, direct exposure of F1 pups to polyhaloalkene presumably only started upon weaning. Furthermore, the reason for not applying whole body inhalation (and including the F1 pups already at PND 5) over all study phases is unknown.

Mortality and clinical signs

No mortality or clinical signs were observed that could be related to treatment with polyhaloalkene. In all generations during pre-mating, feed consumption, and body weight development were slower in treated groups vs. controls. In the great majority of cases, these deviations were in the range of ca. 5%, only occasionally approaching or reaching ca. 10%. **Error! Reference source not found.** includes terminal body weight data of all groups upon sacrifice.

Table 15

TERMINAL BODY WEIGHT DATA (G ± S.E.) FROM THE MULTIGENERATION STUDY WITH POLYHALOALKENE IN RATS (TNO, 2011)				
Dose level (ppm)	**0**	**5000**	**15000**	**50000**
F0 males				
Absolute	352.7 ± 4.30	330.3** ± 5.32	325.7# ± 4.16	327.0# ± 4.95
Relative to control (%)	100	94	92	93
F0 females				
Absolute	265.6 ± 1.99	263.1 ± 2.43	260.8 ± 2.47	254.4* ± 2.88
Relative to control (%)	100	99	98	96
F1 males				
Absolute	314.2 ± 5.39	286.2 ± 5.15	279.1 ± 5.34	283.1 ± 3.44
Relative to control (%)	100	91	89	90
F1 females				
Absolute	245.7 ± 2.88	242.8 ± 3.64	235.8 ± 3.05	237.3 ± 4.63
Relative to control (%)	100	99	96	97

* $p < 0.05$, **$p < 0.01$, # $p < 0.001$

Due to the limited extent of the feed consumption and body weight changes, these effects were not considered as adverse by themselves. However, effects on the development of the offspring noted at the mid- and high-dose levels correlated with body weight development and at these dose levels adversity was assumed (see below for a more detailed analysis).

Reproductive parameters

Pre-coital time and duration of gestation were prolonged in all treatment groups vs. the corresponding in-study controls. Duration of gestation was found outside the range of historical control means in all treatment groups of both the F0 and F1 generations. However, this also holds for the F0 control group. Mean pre-coital time was outside the

historical control mean range in the F0 low- and high-dose groups (but the increase was statistically significant only in the F0 mid-dose group). In the F1 generation, this parameter was increased, but remained within the limits of the historical control range, with statistical significance obtained at 15000 and 50000 ppm. Table 16 summarises these findings.

Table 168

EFFECT OF POLYHALOALKENE ON PRE-COITAL TIME AND DURATION OF GESTATION IN THE MULTIGENERATION STUDY WITH RATS (TNO, 2011)					
Dose level (ppm)	**0**	**5 000**	**15 000**	**50 000**	**Historical control**
F0					
Pre-coital time (mean ± sd, d)	2.27 ± 0.258	3.44* ± 0.322	3.39* ± 0.350	3.50* ± 0.387	2.04-3.43 (n=22)
Duration of gestation (mean ± sd, d)	21.56 ± 0.101	21.92* ± 0.055	21.86 ± 0.067	21.92* ± 0.055	21.04-21.52 (n=22)
F1					
Pre-coital time (mean ± sd, d)	2.07 ± 0.226	2.81 ± 0.319	3.12** ± 0.285	3.27** ± 0.252	2.04-3.43 (n=22)

* p < 0.05, **p < 0.01

All in all the changes appear only slight with respect to the historical control ranges. Moreover, reproductive outcome was unaffected by polyhaloalkene treatment, therefore the biological significance or adversity of these effects is unclear.

All other investigated parameters (oestrus cyclicity, mating index, fecundity index) did not show treatment-related deviations from the corresponding in-study controls.

Effects on offspring

In F1 females, an apparent delay in the onset of puberty as expressed by delayed vaginal opening, was observed (Table 17).

Table 17

EFFECT OF POLYHALOALKENE ON THE ONSET OF PUBERTY IN F1 FEMALES IN THE MULTIGENERATION STUDY WITH RATS (TNO, 2011)					
Dose level (ppm)	**0**	**5 000**	**15 000**	**50 000**	**Historical controls (n=4)**
Percentage of animals reaching criteria	100	100	96	100	92-100
Day reaching criteria for vaginal opening (mean ± S.E.)	39.36 ± 0.753	40.36 ± 0.779	42.48* ± 0.963	43.46** ± 0.836	36.9-39.6

* p < 0.05; ** p < 0.01

A graphical representation of the changes is given in Fig. 1. The box plot shows that the effect becomes more clearly visible when considering median and not arithmetic mean. However, even the mean number of days needed to reach the criteria for vaginal opening was outside the range of historical controls in all treatment groups. Statistical significance was obtained for the mid- and high-dose groups only.

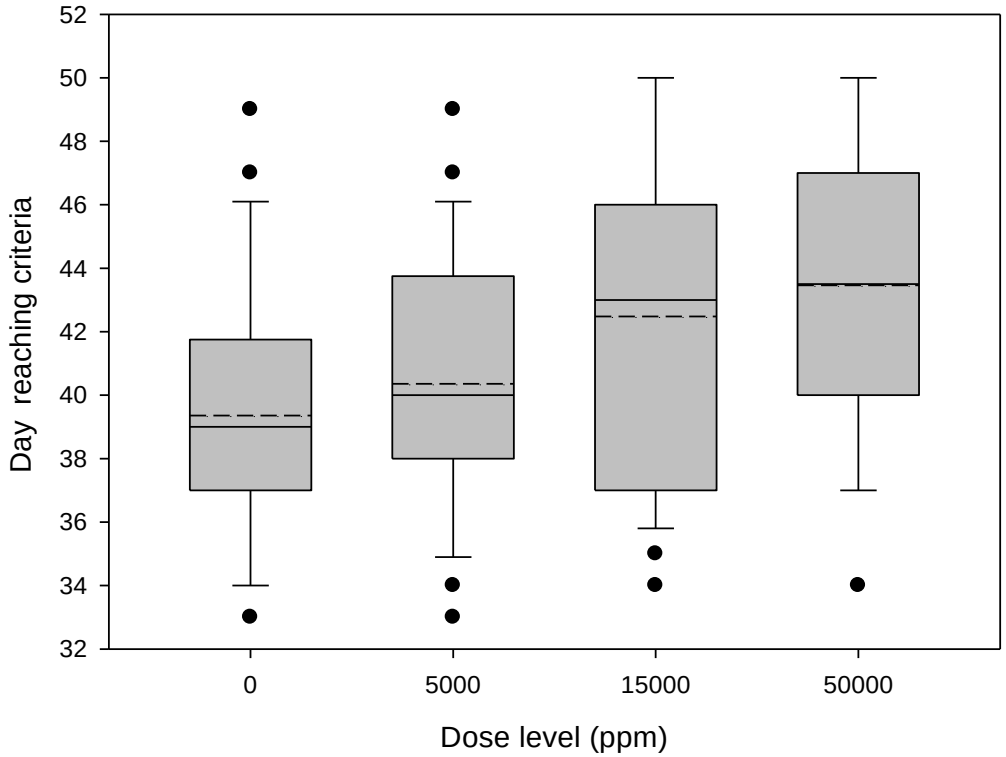
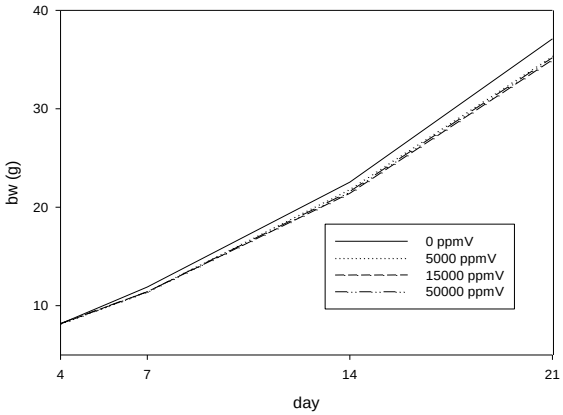


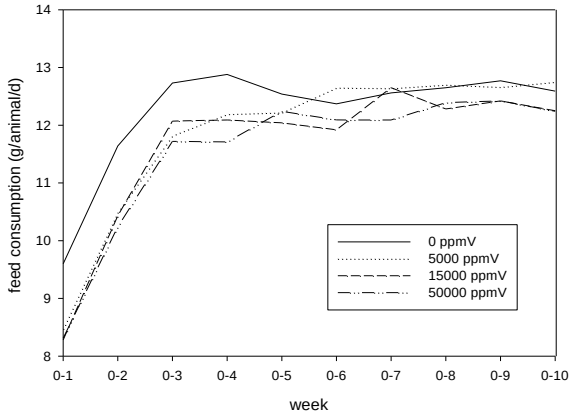
Fig. 1: Box plot of the effects of polyhaloalkene on vaginal opening in female F1 rats (based on data from (TNO, 2011)). Lines within boxes: solid = median, dashed = arithmetic mean. The number of animals included was 28/group except for the 15000 ppm group, where one animal was left out which did not reach the criteria until and including day 60.

The study author argued that this finding was not a direct effect, but was related to the decreased body weight development of this group. A detailed graphical representation of the respective body weight and feed consumption data is given in **Error! Reference source not found.** (next page).

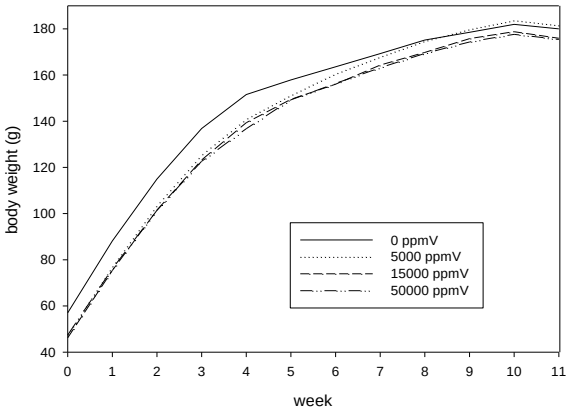


a) body weight PND 4 (pre-culling) - PND 21:

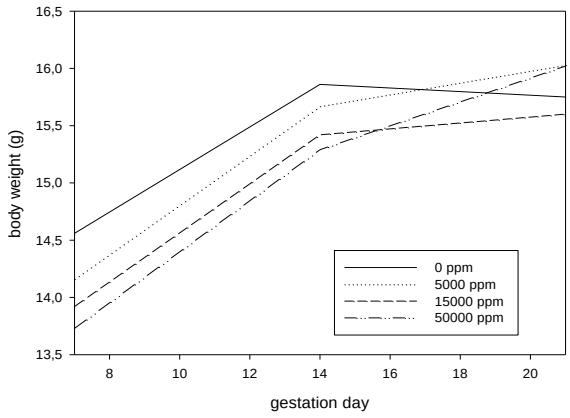
b) feed consumption during pre-mating:



c) body weight during pre-mating:



d) feed consumption during gestation:



e) body weight during gestation:

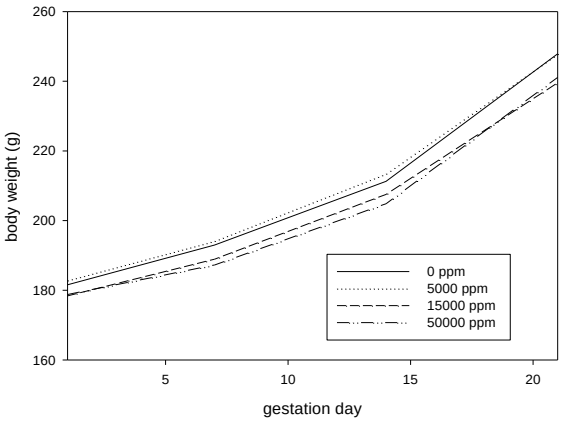


Fig. 2: Body weight and feed consumption during different life stages of the F0 pup/F1 females from PND 4 until the end of gestation (based on data from (TNO, 2011))

In **Error! Reference source not found.** c), indeed a delay of body weight development is noticeable until about week 6 of the pre-mating phase for these animals. Moreover, the authors reported that when an analysis of covariance (ANCOVA) was performed including pup weight at PND 21 [cf. **Error! Reference source not found.** a)] as a covariate, statistical significance was only reached for the high-dose group. This is remarkable because mean F0 pup weight at PND 21 was only slightly lower than those of the controls (by 4, 5, and 5% at 5000, 15000, and 50000 ppm) and this deviation was not statistically significant by itself.

Following this line of argumentation, the delay of vaginal patency at the mid-dose group would be fully explainable by the difference in body weight at PND 21, whereas the delay by yet another day (vs. the mid-dose group) in the high-dose group would not be completely explained.

Based on this reasoning, the study author upon finalising the report in 2009 concluded that 15000 ppm was the NOAEC and 50000 the LOAEC for vaginal opening.

Due to a request by the study sponsor, a re-assessment was performed in an amendment to the study report in 2011. The author now argued that lower feed consumption and body weight observed in adolescent F1 animals until week 4 of pre-mating [cf. **Error! Reference source not found.** b) and c)] would serve as further evidence for ruling out a direct effect of polyhaloalkene on maturation. Therefore, the NOAEC was raised to 50000 ppm (the highest dose tested). This argument does not appear valid as feed consumption and body weight during weeks 0 to 4 of pre-mating were comparable in all treated groups and thus cannot explain the differences observed between these groups.

The eMSCA considers a delay of puberty to the extent observed in the mid- and high-dose groups as an adverse effect. The female pre-pubertal assay is part of the Tier 1 testing strategy for endocrine disruptors as established by the US EPA's Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC). A comprehensive review on the highly complex mechanisms of regulating sexual maturation, focusing on hormonal regulation and its perturbation by diverse endogenous and xenobiotic agents via a variety of mechanisms was provided by (Goldman et al., 2000). Some aspects will be discussed in more detail below in section 7.15.

Moreover, regardless of whether the effect is regarded as an indirect result of treatment-related decreased body weight gain or as a direct outcome of polyhaloalkene treatment, it still remains an effect that is considered adverse and should be used as the basis for setting the NOAEC. In summary it is concluded that:

- Delay of puberty to the extent observed in the mid- and high-dose groups (i.e. by three and four days vs. control, respectively) is rated as an adverse effect.
- At the mid-dose level, a possible explanation for the observed delay is provided by the slightly reduced body weight (vs. controls) observed on PND 21. However this deviation was small, not statistically significant by itself and it did not lead to a comparable delay in maturation of male F0 pups.
- Notably, this decrease in body weight, while not being considered adverse by itself, follows a dose-related trend. It is also consistent with the slight reduction in body weight gain observed in all treated groups over the whole range of the study. Thus, although perhaps being caused by an indirect, but nevertheless substance-related mechanism, also the delay in vaginal opening at the mid-dose level is rated as a substance-related adverse effect.
- At the high-dose level, the observed reduced body weight alone was found not to sufficiently explain the observed delay. Therefore, while evidence for a specific mechanism is lacking, a direct substance effect of polyhaloalkene on sexual maturation cannot be ruled out.

Based on these considerations, the NOAEC for pubertal delay in female rats is set at the low dose level, i.e. at 5000 ppm.

Pup findings

In F1 pups (F2 generation), the number of runts (defined as pup weight less than mean pup weight of the control group minus two standard deviations) was increased in a dose-related fashion with statistical significance in all treated dose groups. However, no such trend was observed with the F0 progeny and absolute numbers of runts in the groups treated with polyhaloalkene were lower than those observed in the F0 in-study control group. This was therefore considered a chance finding not likely to have been caused by substance administration. In addition, the number of pups lost (dying, missing, and/or cannibalised) during PND 1-4 was significantly increased at 50000 ppm. Half of the lost pups at this dose level came from one litter which was lost entirely (

Table 18).

Table 18

EFFECTS OF POLYHALOALKENE ON F1 PUPS (NUMBER OF AFFECTED LITTERS) IN THE MULTIGENERATION STUDY WITH RATS (TNO, 2011)				
Dose level (ppm)	**0**	**5 000**	**15 000**	**50 000**
No. litters	27	25	25	27
No. live-born pups, PND 1	246	218	222	236
Runts on PND 1, F1: No./%	0	5*(3)/ 2.3 (12)	6*(1)/ 2.7 (0.5)	10# (4)/ 4.2 (14.8)
Pups lost during PND 1-4, F1: No./%	2 (2)/ 0.8 (7.4)	6 (3)/ 2.8 (12)	4 (2)/ 1.8 (8.0)	20# (6)/ 8.5 (22.2)

* p < 0.05, ** p < 0.01. # p < 0.001

Conclusion

The overall NOAEC for the multigeneration study in rats (TNO, 2011) is 5000 ppm based on delayed onset of vaginal opening at dose levels greater than or equal to 15000 ppm.

7.9.7.4.2. Human information

No human data on the potential of polyhaloalkene for impairing fertility are available.

7.9.7.5. **Developmental toxicity**

7.9.7.5.1. Non-human information

Two studies on pre-natal development in rats (TNO, 2007) and rabbits (WIL, 2011a) are available which are summarised in Table 19.

7.9.7.5.1.1. Pre-natal development study in rats (TNO, 2007)

Maternal toxicity

In the study in rats, no mortality, clinical signs, or macroscopic pathological findings caused by treatment of parental animals with polyhaloalkene were observed. Maternal body weight or feed consumption were unaffected by treatment. Likewise, no dose-related, statistically significant deviations from control with respect to reproduction parameters were observed. The mean number of total resorptions per animal was slightly increased from 0.42 in the control group to ca. 1 in the treated groups, but this finding was without statistical significance. There were no treatment-related changes in the weight of (female) reproductive organs.

Offspring toxicity

Placenta weight was increased by 15-20% in all treated groups with statistical significance vs. controls. Due to a different test design, comparable data from the multigeneration study in rats are not available. The biological significance of this finding is not clear and adversity cannot be clearly established.

Mean foetus weight was slightly, but consistently decreased in all treatment groups. However, changes vs. controls were only small, did not reach statistical significance and also similar findings had not been observed in the multigeneration study in rats (cf. previous section).

Despite the fact that foetus weight was not significantly changed, the number of small foetuses (foetuses with < 75% of the mean control group body weight) was increased in a dose-related manner, with statistical significance reached at 15 000 ppm. Also in absolute terms, numbers were higher than those observed in the control groups of the multigeneration study in rats (cf. previous section).

Table 19

OVERVIEW OF AVAILABLE STUDIES ON DEVELOPMENTAL TOXICITY WITH POLYHALOALKENE						
Method/ guideline	**Route**	**Species, strain, sex, no/group**	**Dose levels (ppm); , exposure scheme**	**Results**	**Remarks**	**Reference**
Pre-natal development toxicity study/OECD 414; GLP; reliability 1 (reliable without restrictions)	Inhalation, nose-only	Rat, Wistar (Crl:WI(WU)BR), F, 22-25 (pregnant)	0 - 5000 - 15000 - 50000; 6 h/d on GD 6-19	No test substance-related effect on mortality, clinical signs, body weight (gain), feed consumption, fecundity index, gestation index, corpora lutea, number of implantation sites, pre- and post-implantation loss, number of live and dead fetuses, number of resorptions, or sex ratio of pups, visceral malformations Maternal toxicity No treatment-related adverse effects Offspring toxicity: ≥ 5000 ppm: Wavy ribs, delayed ossification, increased placenta weight; ≥ 15000 ppm: increased incidence of small foetuses **$NOAEC_{maternal}$:** 50000 ppm **$NOEC_{development}$:** ≤ 5000 ppm **$NOAEC_{development}$:** 5000 ppm	None	(TNO, 2007)

OVERVIEW OF AVAILABLE STUDIES ON DEVELOPMENTAL TOXICITY WITH POLYHALOALKENE						
Method/ guideline	**Route**	**Species, strain, sex, no/group**	**Dose levels (ppm); , exposure scheme**	**Results**	**Remarks**	**Reference**
Pre-natal development toxicity study/OECD 414; GLP; reliability 1 (reliable without restrictions)	Inhalation, whole body	Rabbit, NZW, F, 24 (12 per phase, cf. remarks)	0-2500-4000/5500-7500; 6 h/d on GD 6-28 Dose levels were set based on a range-finding experiment with maternal toxicity at ≥ 10000 ppm	Maternal toxicity No clinical signs indicative of an acute substance effect; ≥2500 ppm: Subacute inflammation of the heart; ≥5500 ppm: Mortality, renal tubular necrosis, premature delivery, abortions; ≥7 500 ppm: Coagulation necrosis of the heart Offspring toxicity ≥ 5500 ppm: Malformations of the heart and the great vessels (strong link to maternal toxicity) **$NOAEC_{maternal}$**: < 2500 ppm **$NOAEC_{development}$**: 4 000 ppm	Dose groups were split into two subgroups each, due to limited space in the exposure chamber. For the group administered 4000 ppm in Phase I, no toxicity was noted, therefore the corresponding group in Phase II received 5500 ppm Furthermore, 4000/5500 ppm groups were run in duplicate with test substance produced at two different production sites (no relevant difference was noted)	(WIL, 2011a; WIL, 2011b)

No treatment-related visceral anomalies or variations were observed. Upon skeletal examination of the foetuses, a treatment-related increase in wavy ribs was observed. Likewise a different ossification profile of diverse parts of the skeleton was noted: As a general trend, for a given part of the skeleton, there were either no significant differences between controls and treated groups, or the degree of incomplete or absent ossification was higher in treated groups vs. controls. These effects were considered treatment-related but were regarded as signs of a slight, reversible delay in development, which usually is not rated as an adverse effect.

All pup findings are summarised in Table 202. For the sake of readability, incomplete or absent ossification of the diverse parts of the skeleton is not included.

Table 20

FINDINGS IN PUPS IN THE PRE-NATAL DEVELOPMENT STUDY WITH POLYHALOALKENE IN RATS (TNO, 2007)				
Dose level (ppm)	**0**	**5000**	**15000**	**50000**
Placenta weight (g)				
All viable foetuses (% vs. control)	0.4547	0.5413** (+19)	0.5434** (+20)	0.5378** (+18)
Male foetuses (% vs. control)	0.4665	0.5600** (+20)	0.5447** (+17)	0.5472** (+17)
Female foetuses (% vs. control)	0.4424	0.5110** (+16)	0.5343** (+21)	0.5234** (+18)
Foetal weight (g)				
All viable foetuses (% vs. control)	4.3274	4.2656 (-1.5)	4.1896 (-3.2)	4.1808 (-3.4)
Male foetuses (% vs. control)	4.4723	4.3958 (-1.7)	4.2285 (-5.5)	4.2743 (-4.5)
Female foetuses (% vs. control)	4.1722	4.0995 (-1.7)	4.1121 (-1.5)	4.0643 (-3.6)
Incidence of small foetuses				
Litters evaluated	24	21	24	25
Foetuses evaluated	267	224	249	266
Litter incidence (%)	0	3 (14)	5** (21)	7** (28)
Foetal incidence (%)	0	4 (1.8)	8** (3.2)	9** (3.4)
Skeletal anomalies				
Litters evaluated	24	21	24	25
Foetuses evaluated	140	116	132	139
Two or more wavy ribs: No. foetuses (%)/no. litters (%)	9 (6.4)/ 6 (25)	41# (35)/ 17# (81)	58# (44)/ 18** (75)	63# (45)/ 24# (96)

* $p < 0.05$; ** $p < 0.01$; # $< p < 0.001$

In summary, the NOEC of this study is < 5000 ppm based on increased placenta weight, skeletal anomalies and delayed ossification. The NOAEC of this study is 50000 ppm for maternal toxicity and 5000 ppm for offspring, based on the increased incidence of small

foetuses. The higher incidence of small foetuses is not regarded as an acute effect, i.e. an effect which can be elicited by a single exposure only.

7.9.7.5.1.2. Pre-natal development study in rabbits (WIL, 2011a)

Maternal toxicity

Dose-related mortality and an increase in abortions were observed in maternal animals (Table 21).

Table 21

MATERNAL MORTALITY, ABORTIONS, AND CLINICAL SIGNS IN THE PRE-NATAL DEVELOPMENT STUDY WITH POLYHALOALKENE IN RABBITS (WIL, 2011A). IN PARENTHESES: DAY(S) OF OCCURRENCE					
Dose level (ppm)	**0**	**2 500**	**4 000**	**5 500**	**7 500**
No. found dead	0	0	0	3 (13, 14, 27)	6 (12, 14, 18, 20)
No. euthanised *in extremis*	0	0	0	1 (28)	1 (16)
Aborted	0	0	0	1 (28)	3 (26, 29)
Delivered	0	0	0	0	1 (29)

On the day of or prior to death or euthanasia, 1 and 3 females in the 5500 and 7 500 ppm groups, respectively, had laboured and/or decreased respiration, 2 females in the 5500 ppm group were hypoactive, 1 female in the 7500 ppm group had clear material around the nose and 1 female in the 7500 ppm group had red material on the left hindlimb. In addition, the female in the 5500 ppm group had red material on the urogenital area on the day prior to euthanasia and 1 occurrence of laboured respiration several days prior to death. No test substance-related clinical findings were noted at the daily examinations of females that survived to the scheduled necropsy, during mid-point of exposure or 1 hour post-exposure at any exposure concentration.

Among the surviving does, one animal in each of the groups ≥ 4000 ppm displayed decreased and/or laboured breathing.

Body weight of does during gestation was not affected by treatment with polyhaloalkene in a dose-related, time-coherent, and statistically significant way. Mean feed consumption (on a g/animal/d basis) was significantly lower in the two top dose groups (by 9 and 21%, respectively) on days 18-19, sometimes also on other occasions, but without a clear dose-related trend.

Macroscopic pathology did not reveal any treatment-related observations. Maternal histo-pathological analysis originally included only animals from the two top dose groups. In the course of the study revision in 2011, tissues of all 24 does from each group were (re-)examined. The results of this analysis and their relationship to unscheduled deaths are summarised in Table 22.

The finding of heart inflammation is considered as a clearly treatment-induced, adverse effect. In this context, the slightly lower incidence in the 5500 ppm group is considered to lie within the limits of a dose-related trend.

The mechanism behind this finding is unknown. A potential hypertensive effect of polyhaloalkene has been suggested in the toxicogenomics study (Hamner Institute, 2008), but proof for this association appears weak. In the 'Product Stewardship Summary' for the substance HFC-245fa (1,1,1,3,3-pentafluoropropane) which is freely available on the internet one of the registrants noted that this substance also caused 'mild inflammation of

the heart'.[10] According to the same source, HFC-245a is also a 'cardiac sensitiser', i.e. it can boost the effect of catecholamines on the heart (which was not established for polyhaloalkene in the corresponding experiment, cf. section 7.10.1.3).

For the findings in kidneys and lungs, the correlation to treatment is less clear, therefore they cannot be ascribed to the test substance with sufficient certainty.

Table 22

INCIDENCE OF SELECTED HISTOPATHOLOGICAL FINDINGS, UNSCHEDULED DEATHS AND SCHEDULED NECROPSY IN DOES FROM THE PRE-NATAL DEVELOPMENT STUDY WITH POLYHALOALKENE IN RABBITS (WIL, 2011A); 24 TISSUES WERE EXAMINED FROM EACH GROUP, INCLUDING BOTH SCHEDULED AND UNSCHEDULED DEATHS					
Dose level (ppm)	**0**	**2 500**	**4 000**	**5 500**	**7 500**
Heart					
Inflammation, subacute (%)	0	8 (33)	12 (50)	10 (42)	15 (63)
Minimal	-	3	1	2	2
Mild	-	2	2	5	6
Moderate	-	3	8	3	6
Severe	-	-	1	-	1
Coagulation necrosis (%)	0	0	0	0	1 (4)
Moderate	-	-	-	-	1
Kidneys					
Necrosis	0	0	0	3	1
Mild	-	-	-	2	-
Moderate	-	-	-	1	-
Severe	-	-	-	-	1
Lungs					
Congestion	0	2	5	3	3
Mild	-	1	1	2	2
Moderate	-	1	4	1	1
Haemorrhage	4	6	3	3	1
Minimal	2	2	-	1	-
Mild	2	4	3	1	-
Moderate	-	-	-	1	1
Inflammation	8	8	8	3	4
Minimal	4	5	6	3	2
Mild	4	3	2	-	2
Alveolar macrophages*	4	10	7	2	3
Minimal	2	6	6	2	3
Mild	1	4	-	-	-
Moderate	1	-	1	-	-
Cause of death					
Undetermined	-	-	-	5	10
Heart inflammation	-	-	-	4	6
Lung haemorrhage	-	-	-	1	3
and oedema	-	-	-	0	1

* Including the incidence of pigmented and non-pigmented macrophages

[10] "HFC-245fa Product Stewardshio Summary, December 2007": http://www51.honeywell.com/sm/common/documents/Public-Ris-Summary-HFC-245fa.pdf accessed 3 February 2020.

Reproductive performance

Gravidity as well as the mean number of viable foetuses, implantation sites, resorptions, pre- or post-implantation losses, and corpora lutea per (surviving) doe were not affected by treatment.

Offspring toxicity

Treatment with polyhaloalkene did not affect the offspring sex ratio. Mean foetal weight was decreased in a dose-related manner from 41.9 g in the controls down to 37.8 g in the 7500 ppm group, but this change by 10% was not statistically significant as it was of the order of the standard deviations observed for all groups. There was no significant difference between the weight of male and female foetuses. Upon visceral examination of the foetuses malformations of the heart and great vessels were observed (Table 23).

Table 23

VISCERAL MALFORMATIONS OF RABBIT FOETUSES FROM THE PRE-NATAL DEVELOPMENT TEST WITH RABBITS (WIL, 2011A). IN PARENTHESES: LITTER INCIDENCES					
Dose level (ppm)	**0**	**2 500**	**4 000**	**5 500**	**7 500**
Number of foetuses evaluated	206 (24)	191 (23)	206 (24)	153 (18)	132 (14)
Total number of malformations in heart or great vessels	0	0	0	4 (2)	11 (2)
Total number of foetuses with malformations in heart or great vessels	0	0	0	2 (2)	2 (2)
Foetuses affected (%)	0	0	0	1.3	1.5
Litters affected (%)	0	0	0	11	14
Bulbous aorta: No./%	0	0	0	1 (1)/ 0.7 (6)	3 (2)/ 2.2 (14)
Stenotic pulmonary trunk: No./%	0	0	0	1 (1)/ 0.7 (6)	3 (2)/ 2.2 (14)
Interrupted aortic arch: No./%	0	0	0	1 (1)/ 0.7 (6)	0
Interventricular septum defect: No./%	0	0	0	1 (1)/ 0.7 (6)	3 (2)/ 2.2 (14)
Tricuspid valve absent: No./%	0	0	0	0	2 (2)/ 1.5 (14.2)

* Including the incidence of pigmented and non-pigmented macrophages

Heart and great vessel malformations (bulbous aorta, stenotic pulmonary trunk, interventricular septal defects [absent septa], absent tricuspid valve and/or interrupted aortic arch) were noted in foetuses of the 5500 and 7500 ppm groups. According to the author, the mean litter proportions for these findings exceeded the maximum mean values in in-house laboratory historical controls.

For this reason and due to the similarity of the findings, the malformations in the cardiovascular system of the 5500 and 7500 ppm group foetuses were considered exposure-related. This raises the question whether the observed malformations can be linked to the maternal toxicity observed at the same dose levels.

According to the literature, development of the great vessels in rabbits is completed between gestation day (GD) 16 and 18. In Fig.3, body weight development of affected does is compared with the corresponding group and control means.

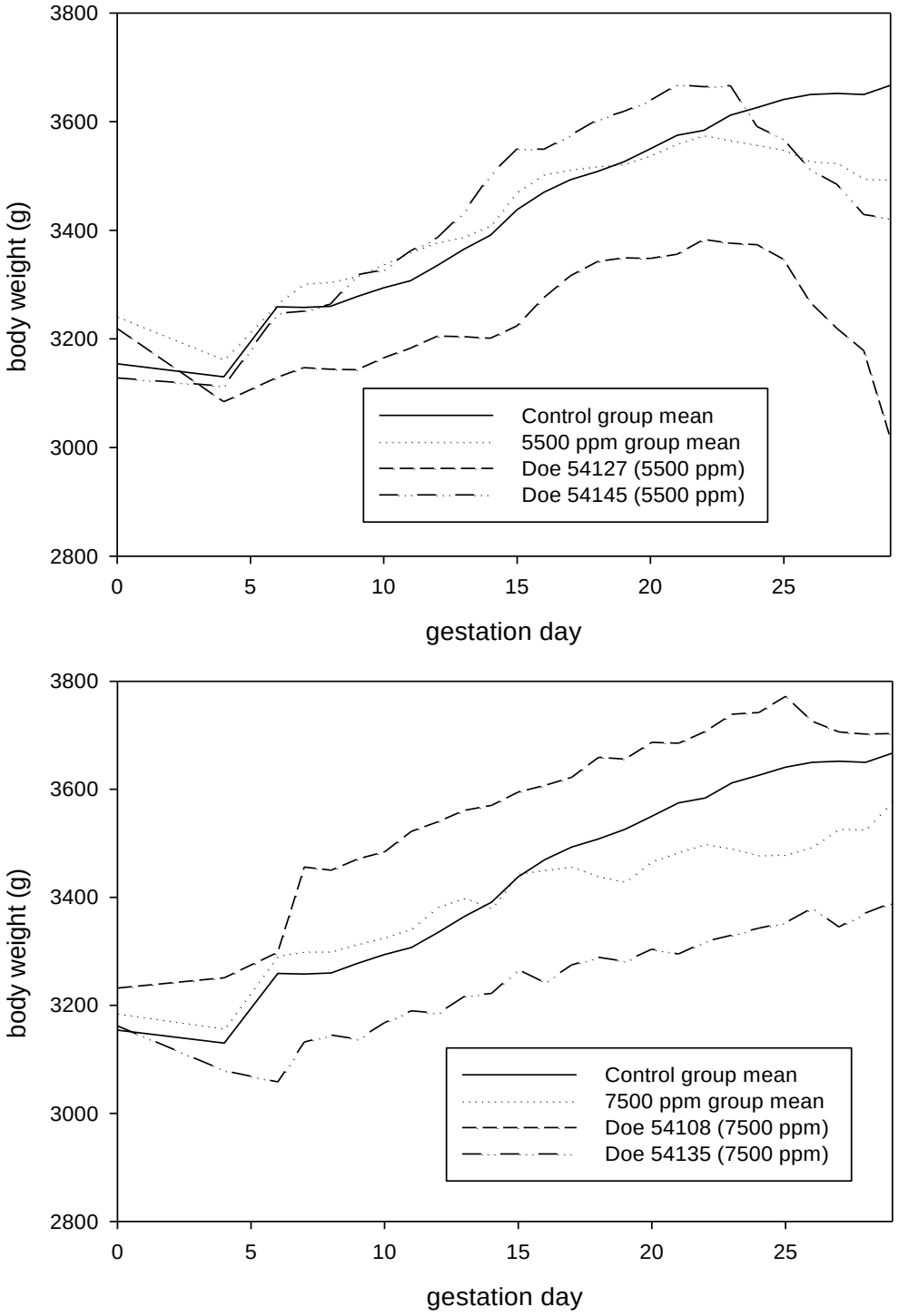


Fig.3: Body weight development during gestation of does bearing foetuses with malformations compared to the corresponding group and control means (based on data from (WIL, 2011a). Above: 5500 ppm, below: 7500 ppm

In the 5500 ppm group, doe 54127 displayed clearly lower than average body weight from GD 4 on. As treatment commenced on GD 6, one could speculate whether this animal started into treatment already in a poor health condition. The stronger than average decline after GD 22 can be attributed to the early resorptions observed with this doe (see below). However, by this time, formation of the heart and great vessels should have been complete. Doe 54145 did not deviate much from the average body weight development of the 5500 ppm group. Between GD 11 and 23, its body weight was even above group and control means. However, the decline in body weight noted for the 5500 ppm group around

GD 23 was also seen in this doe and its terminal body weight amounted to only 93% of the control mean.

At 7500 ppm, doe 54108 displayed a higher than average body weight (also clearly above control mean) throughout GD 7-29, which illustrates in general the variability in the groups. In contrast, doe 54135 showed an atypical weight loss between GD 4-7, but from then on developed in parallel with group and control means.

While based on experience it appears doubtful in general whether maternal weight reduction can result in foetal malformations (Nitzsche, 2017), due to the limited extent of the body weight deviations (all below 10% vs. controls) and the variability among the four affected does, these data cannot establish sufficient proof that the foetal malformations of heart and great vessels can be linked to maternal toxicity.

Table 24 summarises clinical and pathology observations in does with foetuses malformed in the heart or great vessels.

All affected maternal animals suffered from moderate inflammation in the heart (accompanied by other indicators of maternal toxicity). This is seen as a confirmation of the adversity and toxicological relevance of this particular finding in maternal animals.

In summary, these data might point at a link between the observed foetal malformations in the heart and great vessels and maternal toxicity. Nevertheless, it is also not possible to rule out a specific teratogenic mechanism.

Other foetal malformations and developmental variations, when observed in the test substance-treated groups, occurred infrequently or at a frequency similar to that in the control group, did not occur in a dose-related manner and/or the values were reported to lie within the test laboratory's historical control data ranges, and were therefore not attributed to the test substance.

Table 24

ALLOCATION TO FOETUSES WITH OBSERVED MALFORMATIONS IN THE HEART OR GREAT VESSELS TO CORRESPONDING DOES AND RELEVANT OBSERVATIONS (WIL, 2011A)

Dose level (ppm)	Doe no.	Doe observations	No. of implantation sites/early resorptions	Foetus no.	Foetus observations
5500	54127	Clinical signs: None relevant Macroscopic pathology: Brain: hydrocephaly Microscopic pathology: Heart: moderate subacute inflammation	8/3	5	Interrupted aortic arch
	54145	Clinical signs: None relevant Macroscopic pathology: Heart: pale Microscopic pathology: Liver: moderate diffuse, periportal vacuolation	7/0	1	Interventricular septum defect; Stenotic pulmonary trunk; Bulbous aorta

ALLOCATION TO FOETUSES WITH OBSERVED MALFORMATIONS IN THE HEART OR GREAT VESSELS TO CORRESPONDING DOES AND RELEVANT OBSERVATIONS (WIL, 2011A)					
Dose level (ppm)	**Doe no.**	**Doe observations**	**No. of implantation sites/early resorptions**	**Foetus no.**	**Foetus observations**
7500	54108	Clinical signs: None relevant Macroscopic pathology; No significant changes Microscopic pathology: Heart: moderate subacute inflammation; Lungs: slight inflammation	10/0	8	Interventricular septum defect; Tricuspid valve absent; Stenotic pulmonary trunk; Bulbous aorta;
				10	Interventricular septum defect; Stenotic pulmonary trunk; Bulbous aorta
	54135	Clinical signs: None relevant Macroscopic pathology: Oviducts: cyst; Lungs: dark red areas Microscopic pathology: Heart: moderate subacute inflammation; Lungs: moderate congestion	9/0	8	Interventricular septum defect; Tricuspid valve absent; Stenotic pulmonary trunk; Bulbous aorta

Conclusion

The dose level of 2500 ppm is a LOAEC for maternal toxicity (subacute inflammation of the heart at this dose level) and a NOAEC for developmental effects (malformations in the heart and great vessels at ≥ 5500 ppm).

7.9.7.5.2. Human information

No data on the effect of polyhaloalkene on the pre-natal development of humans are available.

7.9.7.5.3. Summary and discussion of reproductive toxicity

7.9.7.5.3.1. Development

Rats

In the study in rats, no adverse maternal effects were seen up to and including 50000 ppm, the highest dose tested.

Already at the lowest dose level of 5000 ppm, treatment-related effects on placenta weight (increase), skeletal anomalies (wavy ribs) and delayed ossification in foetuses were seen. However these findings were not rated as adverse based on their unclear biological relevance (placenta weight) or known reversible nature. At 15000 ppm and above, the incidence of small foetuses was increased. However, classification/labelling with respect to developmental toxicity is not indicated.

The NOAECs derived from this study are 50000 ppm for maternal toxicity and 5000 ppm for offspring, based on the increased incidence of small foetuses.

Rabbits

In the study in rabbits, strong maternal toxicity was observed. Does suffered from moderate, subacute inflammation of the heart already at 2500 ppm, the lowest dose tested. At and above 5000 ppm, renal necrosis, premature delivery, abortions, and mortality occurred. In addition, at 7500 ppm, one doe showed coagulation necrosis of the heart. In the offspring, treatment-related malformations in the heart and great vessels were observed at 5500 and 7500 ppm, however with a link to maternal toxicity which leads to the conclusion that the pre-requisites for a classification/labelling with respect to developmental toxicity are not fulfilled.

The NOAECs derived from this study are < 2500 ppm for maternal and 2500 ppm for offspring toxicity/teratogenicity.

7.9.7.5.3.2. Fertility

In the two-generation study in rats, treatment-related slight reductions in feed consumption and body weight gain vs. control in all treatment groups at various time-points were noted already at the lowest dose level of 5 000 ppm. However, they were not considered adverse by themselves due to their limited size.

At the same dose level, polyhaloalkene treatment also caused an increase in pre-coital time (F0) and an increase in the duration of gestation (F0). Again, the extent of these findings was limited and their adversity was questioned in light of the fact that reproductive performance was not disturbed.

At ≥ 15 000 ppm, treatment with polyhaloalkene resulted in a significant delay in the onset of puberty (vaginal opening) in F1 females, increase in pre-coital time (F0 + F1), and also prolonged duration of gestation (F0+F1).

At 50 000 ppm, the number of F1 pups lost was significantly increased.

In this study, the dose level of 5000 ppm was a LOEC for effects on feed consumption, body weight, increase in pre-coital time, and increase in gestation length. The same dose level was set as the NOAEC of this study, based on delayed vaginal opening in F1 females at 15000 and 50 000 ppm.

Based on the above results, no classification/labelling of polyhaloalkene is warranted.

7.10. Other effects

7.10.1. Non-human information

7.10.1.1. **Neurotoxicity**

No specific data regarding a possible neurotoxic potential of polyhaloalkene are available. Decreased respiration rates were observed in two acute toxicity studies in rats and mice and also in the pre-natal development study in rabbits; these effects (in the acute studies) were termed "anaesthetic" by the registrant. However, there is no further information available that could corroborate this hypothesis and other mechanisms (such as a direct effect on the lungs) can be imagined. Thus, in the absence of any further respective findings in the whole database available for polyhaloalkene, there is currently no indication of a specific neurotoxic or relevant narcotic potential of polyhaloalkene.

7.10.1.2. **Immunotoxicity**

No specific data on the potential immunotoxicity of polyhaloalkene are available. There is also no indication that polyhaloalkene could possess such a potential.

7.10.1.3. **Specific investigations: Other studies**

Fluorinated hydrocarbons are known to exert an effect called "cardiac sensitisation", a term which basically refers to an increased sensitivity of the myocardium towards catecholamines. Design and results of a corresponding test performed in dogs are summarised in Table 25. No effect of polyhaloalkene on cardiac sensitisation was observed at concentrations ≤ 120 000 ppm.

Table 25

SUMMARY OF THE STUDY ON CARDIAC SENSITISATION WITH POLYHALOALKENE (WIL, 2006)						
Method/ Guideline	**Route**	**Species, Strain, Sex, No/group**	**Dose levels (ppm), Duration of exposure**	**Results**	**Remarks**	**Reference**
Cardiac sensiti-sation/no specific guideline; GLP	Inhalation, muzzle only	Dog, beagle, M, 6	20 000-60 000-120 000 Epinephrine challenge administered in the middle of a 10 min exposure to the test article	No indication of cardiac sensitisation No effects on mortality, clinical signs, or body weight **NOAEC**: 120000 ppm	Each dog served as its own control (an ECG was recorded following a pre-exposure epinephrine dose)	(WIL, 2006)

There appears to be no standardised test protocol for this endpoint. When the toxicity database for polyhaloalkene was reviewed in the course of the Gradient phase III study (Gradient, 2009b), some less common aspects of the study design (e.g. choice of criteria for an effect) were noted. The authors conclude:

"The cardiac sensitization study conducted for polyhaloalkene may have been somewhat different in design than tests previously published in the literature […]. The study used baseline levels of epinephrine doses in some dogs that did not produce any arrythmiogenic effect ("the highest dose level tested during the pre-study evaluation that did not elicit significant findings (e.g. PVC)") rather than a minimally arrythmiogenic effect (the term used in previous studies). In addition […] WIL used the criterion of eleven or more premature ventricular contractions in 10 seconds to identify an adverse effect. This particular criterion has not been cited elsewhere. These study design differences would be expected to have fairly limited effects on the final outcome of the study […]. In discussions [...] about the cardiac sensitization study, the company indicated that the study was conducted in the same manner as previous studies and that differences in terminology ("minimally arrythmiogenic" vs "no significant ECG findings") do not indicate differences in study design." (Gradient, 2009b)

These conclusions appear plausible, and therefore the eMSCA concurs with this analysis.

7.10.1.4. **Specific investigations: Thermal degradation products of polyhaloalkene**

When in contact with a flame or a hot surface under certain conditions, polyhaloalkene can decompose to yield the highly irritant/corrosive breakdown products, hydrogen fluoride (HF) and carbonyl difluoride (COF_2).

Hydrogen fluoride (HF)

In the context of this dossier, it was not possible to perform a generic full-scale hazard assessment of hydrogen fluoride. Besides, a number of reviews of the toxicity of hydrogen fluoride by national and international bodies are available (European Commission, 2001; MAK Commission, 2006; NRC, 2004).

There are two major lines of toxic action which have been experimentally confirmed for hydrogen fluoride both in humans and animals, i.e.

- irritation/corrosion after acute or repeated exposure and
- skeletal fluorosis following an increase of fluoride levels in tissues and body fluids, after prolonged exposure.

In this dossier, the toxicity of hydrogen fluoride is characterised against the background of a scenario in which HF is generated following heating/ignition of polyhaloalkene released in an accidental or leakage situation. For this reason, only the acute toxic effects of HF (i.e. irritation/corrosion) and COF_2 after exposure via inhalation are considered, while fluorosis after prolonged exposure is regarded as irrelevant in the frame of this substance evaluation. Above-mentioned reviews confer a deeper insight in HF/fluoride toxicity.

Table 26 shows the results of the relevant studies in humans and animals selected for deriving acute DNELs for HF. Based on the above data, the following relevant NOAECs for HF were established:

- For mild to moderate, reversible irritation: a NOAEC of 2 ppm in healthy adult men (Largent, 1960; Lund et al., 1997; Lund et al., 1999).
- For severe, potentially irreversible damage: a NOAEC of 1589 ppm for 2 min exposure and a NOAEC of 950 ppm for 10 min exposure (Dalbey et al., 1998).

These values are the same that have been used e.g. by the US National Research Council (NRC) as PoDs for setting Acute Exposure Guideline Levels (AEGLs, see (NRC, 2004)) or by the German MAK Commission (MAK Commission, 2006) when setting occupational health limits for HF.

Aside from the above PoDs for mild to moderate, reversible irritation and severe tissue damage, the Gradient phase III study (Gradient, 2009b) also raises the issue of a "tolerance limit", i.e. the question of whether an HF concentration can be determined above which the irritant effects become so intolerable, that any exposed person would feel an overpowering urge to leave the exposure zone immediately.

The latter point (i.e. behaviour of exposed persons in an emergency situation) will be discussed elsewhere in this report. Regarding the tolerance limit, the eMSCA is of the opinion that such a limit is difficult to assign based on the available data. Nevertheless, in spite of already marked symptoms, up to 60 ppm were apparently tolerated for several minutes, and up to 122 ppm for 1 min by probands whose motivation might be assumed to consist of no more than the wish to show a good compliance as test candidates (Machle et al., 1934).

Table 26

OVERVIEW OF STUDIES ON THE ACUTE TOXICITY/IRRITANCY/CORROSIVITY OF HYDROGEN FLUORIDE WITH RELEVANCE FOR SETTING THE DNELS FOR ACUTE HF EXPOSURE		
Test design	**Effects**	**Source**
Human data		
Various concentrations administered to probands, no experimental details	32 ppm: Discomfort, but atmosphere could be tolerated for several minutes, smarting in the nose and eyes was mild, no coughing or sneezing in 3 minutes even though there was	(Machle et al., 1934)

OVERVIEW OF STUDIES ON THE ACUTE TOXICITY/IRRITANCY/CORROSIVITY OF HYDROGEN FLUORIDE WITH RELEVANCE FOR SETTING THE DNELS FOR ACUTE HF EXPOSURE		
Test design	**Effects**	**Source**
	an irritation of the larger air passages, taste of the gas noted after a short time 61 ppm: No smarting of the skin, definite conjunctival irritation, 'quite marked' nasal irritation. Tickling and discomfort in larger air passages noticeable with each inspiration, taste definite 122 ppm: Highest concentration that two men tolerated for more than 1 minute. Definite smarting of the exposed skin in less than 1 minute, conjunctival irritation marked but bearable, taste of the gas pronounced	
Six experiments with five volunteers, 10-50 days at 0.9-8.1 ppm	Up to 2 ppm: Slight stinging sensation in eyes and facial skin, slight irritation of the nasal passages 3.39 ppm and higher: Redness of facial skin, sour taste in the mouth	(Largent, 1960)
20 healthy male volunteers, age 21-44, exposed to HF for 1 h at ≤ 0.7 ppm, 0.9-2.9 ppm, and 3.1-6.4 ppm*	> 0.7 ppm: Increased fluoride plasma levels > 3.1 ppm: Pronounced symptoms from the upper respiratory tract Upper airway symptoms of low severity present already in the lowest treatment group, and increased in incidence and severity with higher dose. No symptoms 24 h post-exposure	(Lund et al., 1997)
19 healthy male volunteers, age 21-44, exposed to HF for 1 h at ≤ 0.7 ppm, 0.9-2.9 ppm, and 3.1-6.4 ppm*	Upon bronchioalveolar lavage (BAL), markers of acute inflammation (lymphocytes, in particular CD3+ cells, myeloperoxidase, IL-6), were increased in all dose groups, but to a greater extent at the higher dose levels (but no clear dose correlation)	(Lund et al., 1999)
Animal data		
20 female SD rats/group exposed to varying concentrations of HF for 2, 10, and 60 min (dose levels chosen to obtain roughly the same C x t products) The majority of groups was trachea-cannulated to simulate mouth-breathing (MB), but some groups were not cannulated (nose-breathing, NB)	**NB** Strongly decreased breathing rate at 1669 ppm x 10 min/6392 ppm x 2 min **MB** 2 min exposure: ≤ 1589 ppm: Mild effects in BAL parameters; ≥ 4877 ppm: Stronger effects in BAL parameters, decreased breathing rate, changes in pulmonary function, mortality 10 min exposure: ≥ 950 ppm: Mild effects, slightly decreased breathing rate; 1764 ppm: 5% mortality, strong increase in BAL parameters (protein, LDH, sialic acid, MPO, PMNs), decrease in lung function, decrease in thymus weight, histology: increased incidence	(Dalbey et al., 1998)

OVERVIEW OF STUDIES ON THE ACUTE TOXICITY/IRRITANCY/CORROSIVITY OF HYDROGEN FLUORIDE WITH RELEVANCE FOR SETTING THE DNELS FOR ACUTE HF EXPOSURE		
Test design	**Effects**	**Source**
A sham-exposed control group of 20 females was included	of midtracheal inflammation and necrosis; 3847 ppm: 50% mortality	

*calculated from concentrations in mg/m^3 by using a conversion factor of 1.223 ppm/(mg/m^3)

Carbonyl difluoride (COF_2)

The eMSCA did not evaluate carbonyl difluoride (also known as "carbonyl fluoride") as part of previous risk assessments. It was also not possible to perform a generic evaluation in the frame of this dossier. The information provided below is cited from various text passages of the evaluation document for setting Acute Exposure Guideline Levels (AEGLs) issued by the US National Research Council (NRC, 2014). Apparently, a final version of this document has not been prepared yet.

The following text is taken verbatim from the NRC document, but the order of text passages has been re-arranged:

"Carbonyl fluoride is the fluorine analogue of phosgene (carbonyl chloride). However, only a small amount of phosgene hydrolyzes when it comes into contact with moisture […], whereas carbonyl fluoride is "instantly hydrolyzed by water" […], The primary mechanism of action of phosgene is acylation resulting in lipid and protein denaturation, irreversible membrane changes, and disruption of enzymatic function.[…]

Carbonyl fluoride is a colorless, irritating gas, with a pungent odor. It is hygroscopic, and is hydrolyzed into carbon dioxide and hydrogen fluoride by water. […] The thermal decomposition of fluoropolymers such as polytetrafluoroethylene and polyfluoro-ethylenepropylene is a major source of exposure because carbonyl fluoride is the major reaction product from the rapid destruction of plastic materials at temperatures above 500 °C. […]

Carbonyl fluoride is a strong irritant to the eyes and respiratory tract. The irritancy of carbonyl fluoride is hypothesized to be due to hydrogen fluoride, a known sensory irritant. However, the toxicity of carbonyl fluoride is greater than that of hydrogen fluoride, and may be the result of deep penetration into the lungs as well as the production of hydrogen fluoride.

[…] Groups of two male ChR-CD rats were exposed to carbonyl fluoride by inhalation at nominal concentrations of 5 or 10 ppm and a group of six rats was exposed at 100 ppm for 4 h. Three rats exposed at 100 ppm died, and pathologic examination showed they had acute tracheobronchitis and pulmonary conges-tion. The surviving rats exhibited no pathologic changes. The 4-h LC_{50} (lethal concentration, 50% lethality) was approximately 100 ppm. No deaths occurred in the groups exposed at lower concentrations. The data were presented in a table of a one-page preliminary report (DuPont, 1959).

(Scheel et al., 1968) evaluated the acute inhalation toxicity of carbonyl fluoride in groups of five male and five female Greenacres Controlled Flora rats (8 and 24 weeks old). Carbonyl fluoride was generated by polytetrafluoroethylene pyrolysis at 550 ºC. The authors referenced work by (Coleman et al., 1968), which identified carbonyl fluoride as a principal toxic component of the pyrolysis gases, as their rationale for using polytetrafluoroethylene pyrolysis to produce carbonyl fluoride. Atmospheres were generated with a metered air stream into the exposure chamber, and concentrations were measured by the hydrolysable fluoride method. Rats were exposed at various concentrations with the lowest being 310 ppm for 1 h, followed by a 14-day observation period. (With the exception of the 310-ppm value, actual concentrations were not provided). Deaths usually occurred within 24 h with few latent deaths. The LC_{50} values for the 8- and 24-week-old rats were 360 and 460 ppm, respectively. Although an age

difference in mortality was apparent, no difference between the sexes was found. Exposure at 310 ppm resulted in focal hemorrhage of the lungs and pulmonary edema, observed 24 h after exposure. The authors stated that those effects were produced at the same concentration in other species, including the dog, rabbit, guinea pig, and mouse, although individual data and photomicrographs of the lungs were not provided for those species. The lungs showed rapid cellular reorganization and clearing of edema 48 h after exposure, but alveolar damage was still present. Extravasation of red cells from damaged capillaries continued for up to 7 days; the effect was accompanied by mild interstitial fibrosis. Although data were not provided, (Scheel et al., 1968) reported that a 4-h exposure at 90 ppm also resulted in approximately 50% mortality.

(DuPont, 1976) exposed male ChR-CD rats (10/group) to carbonyl fluoride (> 97% pure) at 26.7, 30.8, 32.7, 41.3, 44.7, 47.2 (48.8 by infra-red analysis), or 47.6 ppm for 4 h. Test atmospheres were analyzed with a fluoride-specific electrode and confirmed by infra-red analysis. Deaths occurred at every concentration. Mortalities in the respective groups were 5/10, 3/10, 3/10, 6/10, 8/10, 9/10, and 6/10. The calculated LC_{50} was 34.3 ppm. The calculated BMC_{01} was 10.4 ppm and the $BMCL_{05}$ was 5.2 ppm. Respiration in the rats varied directly with exposure concentration and ranged from rapid shallow breathing to convulsive respiration. Pathologic examination revealed white plaques, red focal spots, and consolidation and edema of the lungs. Liver congestion and bright red spleens were also found.

Groups of four male albino rats were exposed to carbonyl fluoride at nominal concentrations of 2.5 or 5 ppm for 2 and 2.5 h in a preliminary investigation of toxicity (DuPont, 1956). The rats were then observed for 24 hr or 8 days. The low concentration 2.5 ppm was not lethal to the rats and no clinical signs developed. At 5 ppm the rats developed slight dyspnea and cyanosis. No other information was reported.

In other studies conducted by (DuPont, 1959) in which groups of two male ChR-CD rats were exposed to carbonyl fluoride at nominal concentrations of 5 or 10 ppm and a group of six rats was exposed at 100 ppm for 4 h. Clinical signs included rapid, shallow respiration and loss of weight in the 5- and 10-ppm groups, but no pathological changes were found. The data were presented in a table of a one page preliminary report.[...]

Summary: Acute inhalation of carbonyl fluoride in rats causes rapid or labored respiration and respiratory irritation, pulmonary congestion and edema, increases in urinary fluoride excretion, proteinuria, and can cause death in rats. Varying LC_{50} values for rats have been reported: 4-h LC_{50} of 34.3 ppm (DuPont, 1976), 90 ppm (Scheel et al., 1968), and 100 ppm (DuPont, 1959), and 1-h LC_{50}s of 360 ppm and 460 ppm for 8-week-old and 24-week-old rats, respectively. The 1-h LC_{50} for hydrogen fluoride in rats is 1 278 ppm (MacEwen and Vernot, 1970). Converting the carbonyl fluoride concentration of 460 ppm to an equivalent concentration of hydrogen fluoride yields a concentration of 867 ppm, which suggests that carbonyl fluoride produces toxicity greater than that caused by hydrogen fluoride released by hydrolysis. Converting the LC_{50} for hydrogen fluoride to an equivalent concentration of carbonyl fluoride gives a predicted value of 680 ppm, nearly 50% greater than that observed. No data on the developmental toxicity, reproductive toxicity, genotoxicity, chronic toxicity, or carcinogenicity of carbonyl fluoride were found." (NRC, 2014). These results are also summarised in Table 27.

Table 27

SUMMARY OF ACUTE INHALATION TOXICITY DATA FOR COF_2 IN LABORATORY ANIMALS (REPRODUCED FROM (NRC, 2014)

Species	Concentration (ppm)	Exposure time (h)	Effect	Reference
Rat	2.5 5.0	2, 2.5	None Slight dyspnea and cyanosis	(DuPont, 1956)
Rat	5 10 100	4	Rapid, shallow respiration Rapid, shallow respiration LC50, pulmonary congestion	(DuPont, 1959)

SUMMARY OF ACUTE INHALATION TOXICITY DATA FOR COF_2 IN LABORATORY ANIMALS (REPRODUCED FROM (NRC, 2014)				
Species	**Concentration (ppm)**	**Exposure time (h)**	**Effect**	**Reference**
Rat 8 wk old 24 wk old 8 wk old	 360 460 90	 1 1 4	 LC_{50} LC_{50} LC_{50}	(Scheel et al., 1968)
Rat	26.7 30.8 32.7 34.3 41.3 44.7 47.2 (48.8 IR) 47.6	4	50% mortality 30% mortality 30% mortality LC_{50} (calculated) 60% mortality 80% mortality 90% mortality 60% mortality	(DuPont, 1976)

The eMSCA notes that the available data point to a higher toxicity of COF_2 as compared with that of HF. This would mean that mixtures of COF_2 and HF are likely to be more toxic than HF alone. Consequently, a higher risk for severe health damage of exposed humans may result.

7.11. Combined effects

No specific information on a potential combined toxic effect of polyhaloalkene with other substances is available.

7.12. Hazard assessment of physico-chemical properties

Chapter 10 of the CSR includes the risk characterization for polyhaloalkene based on physic-chemical properties. The registrant only provided a short conclusion on the risk of ignition and the results refer to the detailed SAE CRP report: *The risk to exposure to ignition of HFO-1234yf in use as a refrigerant in automotive applications has been evaluated to be 9.5E-15 events/vehicle operating hour (0.0000095 ppb per vehicle operating hour). The normal EU passenger/occupant spends on average 570 hours per year in their automobile which over a year of operation the risk to exposure of a HFO-1234yf initiated flame is 0.0054 ppb/yr.*

Upon review of the SAE CRP report in order to assess the possible risk of ignition, it is noted (see page 51):

'The finding that HFO-1234yf- oil mixture could be ignited at 750 °C was used by the OEMs in establishing probabilities for the fault tree evaluating the under hood fire scenarios.'

The autoignition temperature (AIT) of flammable gases or liquids is the lowest surface temperature measured in a glass flask by a method prescribed for its determination, at which the developing of an inhomogeneous gas/air or a vapor/air mixture will just be stimulated to burn as a flame. The AIT of polyhaloalkene is 405 °C (EU Method A.15). In order to have a real-world situation in the risk assessment to quantify the hazard due to combustion of a polyhaloalkene-air mixture inside an engine compartment the registrants concluded that the hot surface ignition temperature of a polyhaloalkene-air mixture is above 1000 °C and the ignition of a polyhaloalkene-oil-air mixture will occur above 700 °C (INERIS Report; Attachment J to the Gradient report). Basically, ignition phenomena on hot surfaces are strongly influenced by the given test conditions considering all real-life influences. It was not stated whether the test conditions that led to the determination of the limiting temperatures of 700° C and 1000 °C, cover all "real-life" conditions (flow

conditions, leakage rates and sizes, contact times etc.) and therefore maximum surface temperatures in excess of the AIT are sufficiently secure.

According to classical explosion protection aspects it is strongly recommended that the maximum surface temperature does not exceed the AIT. Such a definition is to find e.g. in the European standard EN 13463-1:2009 "Non-electrical equipment for use in potentially explosive atmospheres – Part 1: Basic method and requirements". This standard specifies the basic method and requirements for design, construction, testing and marking of non-electrical equipment intended for use in potentially explosive atmospheres in air of gas, vapour, mist and dusts. The definitions and requirements can be transferred to the conditions in an engine compartment and the establishment of the maximum surface temperature in an application is acceptable:

"Where the equipment is intended and marked for use only with one or more specific gas or vapour explosive atmospheres, then the maximum surface temperature shall not exceed the lowest ignition temperature of those explosive atmospheres."

The assessment of the ignition temperature affects the potential ignition sources in the engine compartment and therefore the occurrence probability of events leading to a possible risk. The registrants should justify why ignition temperatures exceeding the AIT are acceptable for the risk analysis and no further conditions can occur, in case of normal operation of the MAC as well as in accidents, which lead to an ignition of the refrigerant at surface temperatures in the range between the AIT and the reported limiting temperatures.

The eMSCA has drawn no final conclusion on the hazard assessment of physico-chemical properties of polyhaloalkene with regard to the auto-ignition temperature as the information requirement of the eMSCA regarding the justification provided by the registrants was removed from the final decision taken by the Commission.

7.13. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

7.13.1. Overview of typical dose descriptors for all endpoints

7.13.1.1. Available dose descriptors for the acute inhalation toxicity of polyhaloalkene

Table 280

AVAILABLE DOSE DESCRIPTORS FOR SETTING AN ACUTE DNEL FOR POLYHALOALKENE					
Study type	**Species**	**Exposure (h/d)**	**Point(s) of Departure (PoDs) for acute effects (ppm)**	**Effects at LOAEC Remarks**	**Reference**
Acute	Rabbit	1	**NOAEC: ≥100000**	No effects up to highest dose tested	(Huntingdon, 2011)
	Mouse	4	LOAEC: 20000 NOAEC: < 20000	Decreased breathing rate, laboured breathing, yellow anogenital staining	(Huntingdon, 2004)
	Rat		LOAEC: 200000 NOAEC: <200000	Decreased breathing rate, laboured breathing, gross pathology (lung)	(TNO, 2006a)

AVAILABLE DOSE DESCRIPTORS FOR SETTING AN ACUTE DNEL FOR POLYHALOALKENE					
Study type	**Species**	**Exposure (h/d)**	**Point(s) of Departure (PoDs) for acute effects (ppm)**	**Effects at LOAEC Remarks**	**Reference**
Subacute (14 d)	Minipig	6	NOAEC: ≥ 10000	No acute effects up to highest dose tested	(Huntingdon, 2013a)
	Rat		**NOAEC: ≥ 50000**		(TNO, 2005d)
Subacute (28 d)	Minipig		NOAEC: ≥ 10000		(Huntingdon, 2014)
	Rabbit		NOAEC: ≥ 5 500		(Huntingdon, 2013b)
	Rat		**NOAEC: ≥50000**		(TNO, 2006b)
Subchronic (90 d)	Rat		**NOAEC: ≥50000**		(TNO, 2009)
Pre-natal development	Rabbit		NOAEC: ≥7500		(WIL, 2011a)
	Rat		NOAEC: ≥50000		(TNO, 2007)
Multigeneration	Rat		NOAEC: ≥50000		(TNO, 2011)

For acute exposures of up to 1 h, the NOAEC of 100000 ppm from the acute inhalation study in rabbits was chosen as the relevant point of departure (PoD) based on the fact that in the acute rat and mouse studies, clinical signs of acute toxicity were only noted three (mice) or two (rats) hours into the study. For exposures between 1 and 6 h, the NOAEC of 50000ppm x 6 h for acute effects in the repeat-dose studies in rats was selected, which was considered to be sufficiently remote from the LOAEC of 200 000 ppm x 4 h in the acute rat experiment. The LOAEC of 20 000 ppm in mice was not considered sufficiently reliable, since only two animals per group were used in that study.

7.13.1.2. **Available dose descriptors for the repeat-dose inhalation toxicity of polyhaloalkene**

Due to the targeting of this SEv to risks arising from the use of polyhaloalkene in vehicles and the absence of relevant exposure scenarios with repeated exposure, a DNEL for subacute, subchronic, or chronic exposure of the general population was not derived.

It is however noted that when setting a chronic DNEL for workers, the registrants make reference to the German OEL (MAK value) of 200 ppm, which is derived from the NOAEC of 500 ppm in the rabbit 28-d study (Huntingdon, 2013b) by assuming an AF of 2.5 based on the following considerations:

- In the rabbit 28 d test, the relevant effects at the LOAEC did not increase much over time and therefore only slight compensation with respect to exposure duration extrapolation appears necessary.
- The rabbit has already proven far more sensitive than other species tested.
- The "preferred value" approach is followed (i.e. give OEL as a decimal of 1, 2, or 5 ppm or mg/m^3).

The eMSCA agrees that the NOAEC of 500 ppm should be the PoD for setting a chronic DNEL and also that an AF for exposure duration extrapolation does not seem to be needed, but notes that the MAK Commission apparently did not take human interindividual variability into account and therefore, if a DNEL for the general population was derived

according to the procedure laid out in the IR & CSA guidance, section R.8, the overall AF should be 25 (2.5 for "other interspecies differences" x 10 for human interindividual variability), resulting in a DNEL of only 20 ppm.Available dose descriptors for the acute toxicity of thermal decomposition products of polyhaloalkene

Table 29

AVAILABLE DOSE DESCRIPTORS FOR SETTING AN ACUTE DNEL FOR HYDROGEN FLUORIDE					
Study	**Species**	**Exposure duration**	**Point(s) of Departure (PoDs) for acute effects (ppm)**	**Effects at LOAEC Remarks**	**Reference**
Volunteer study	Human	10-50 d	NOAEC: 2	Redness of facial skin	(Largent, 1960)
Volunteer study	Human	1 h	NOAEC: 0.7	Pronounced irritation of the upper respiratory tract	(Lund et al., 1997; Lund et al., 1999)
Acute inhalation study	Rat	2 min 10 min	NOAEC: 1589 NOAEC: 950	Mortality, lung effects, BAL parameters Mortality, lung effects, BAL parameters, midtracheal inflammation	(Dalbey et al., 1998)

As the PoD for mild to moderate, but reversible irritation caused by HF, a NOAEC of 2 ppm was derived from the human database. The NOAECs of 950 or 1589 ppm for 10 and 2 min exposure from the study in rats by Dalbey et al. (1998) were selected with a view to severe tissue damage and mortality.

For COF_2, the available studies for acute toxicity have already been summarised in Table 27 above. Both the LC_{50} of 34.3 ppm and the calculated $BMCL_{05}$ of 5.2 ppm from the inhalation study in rats by DuPont (1976) can be used as the basis for deriving a DNEL.

7.13.2. Selection of the critical DNEL(s)/DMEC(s) and/or qualitative/semi-quantitative descriptor for critical health effects

7.13.2.1. DNELs for single, acute exposure of the general population to polyhaloalkene

A DNEL of 4000 ppm for a 1-hr exposure is obtained by starting with the NOAEC of 100000 ppm from the acute inhalation study in rabbits and applying an assessment factor (AF) of 2.5 for inter- and an AF of 10 for intraspecies variability (overall AF: 25).

A DNEL of 2000 ppm for a 6 h exposure is obtained by starting with the NOAEC of 50000 ppm from the repeat-dose inhalation studies in rat and applying an assessment factor (AF) of 2.5 for inter- and an AF of 10 for intraspecies variability (overall AF: 25).

DNELs for other exposure durations can be obtained by time extrapolation using Haber's law: $C^n \times t = \text{const.}$

For extrapolation to shorter durations, n is set to 3. For example, the NOAEC for a 30 min exposure based on the NOAEC for 1 h exposure is calculated as follows:

$$NOAEC_{30\,min} = \sqrt[3]{(NOAEC_{60\,min})^3 * (60\,min/30\,min)}$$

The above 1 h-DNEL was used for extrapolation to t < 1 h, whereas all other extrapolations for acute toxicity were performed based on the 6 h-DNEL. An overview of the results of these calculations is given in Table 30.

Table 30

OVERVIEW OF DNELS FOR POLYHALOALKENE OBTAINED FOR VARIOUS DURATIONS OF SINGLE, ACUTE EXPOSURE			
Exposure duration	**(Converted) NOAEC (ppm)**	**Overall AF**	**DNEL (ppm)***
5 min	229000	25	9200
15 min	159000	25	6400
30 min	126000	25	5000
1 h	100000	25	4000
2 h	72112	25	2900
4 h	57236	25	2300
6 h	50000	25	2000

* values are rounded to hundreds

It is noted that apparently in the risk assessments performed by SAE (Gradient, 2009a; Gradient, 2009b; Gradient, 2013), a so-called Acute Toxicity Exposure Limit (ATEL) of 100000 ppm was used following Standard 34 of the American Society of Heating, Refrigerating and Air-Conditioning Engineers (ASHRAE) as the reference point for risk characterisation with respect to acute toxicity. As Table 30 shows, this value is much higher than the values derived following the rules for DNEL establishment under REACH.

7.13.2.2. **DNELs for repeated exposure of the general population to polyhaloalkene**

Due to the targeting of this SEv to risks arising from the use of polyhaloalkene in vehicles and the absence of relevant exposure scenarios with repeated exposure, a DNEL for subacute, subchronic, or chronic exposure of the general population was not derived.

It is however noted that when setting a chronic DNEL for workers, the registrants make reference to the German OEL (MAK value) of 200 ppm which is derived from the NOAEC of 500 ppm in the rabbit 28-d study (Huntingdon, 2013b) by assuming an AF of 2.5 based on the following considerations:

- In the rabbit 28-d test, the relevant effects at the LOAEC did not increase much over time and therefore only slight compensation with respect to exposure duration extrapolation appears necessary.
- The rabbit has already proven far more sensitive than other species tested.
- The "preferred value" approach is followed (i.e. give OEL as a decimal of 1, 2, or 5 ppm or mg/m^3).

The eMSCA agrees that the NOAEC of 500 ppm should be the PoD for setting a chronic DNEL and also that an AF for exposure duration extrapolation does not seem to be needed, but notes that the MAK Commission apparently did not take human interindividual variability into account and therefore, if a DNEL for the general population was derived according to the procedure laid out in the IR & CSA guidance, section R.8, the overall AF should be 25 (2.5 for "other interspecies differences" x 10 for human interindividual variability), resulting in a DNEL of only 20 ppm.

7.13.2.3. **DNELs for single, acute exposure to hydrogen fluoride**

In the Gradient phase III study (Gradient, 2009b), acute exposure to HF was assessed against the so-called 'Acute Exposure Guideline Levels' (AEGLs) set by the United States National Research Council. AEGLs are defined as follows (text taken from (NRC, 2004)):

"AEGLs represent threshold exposure limits (exposure levels below which adverse health effects are not likely to occur) for the general public and are applicable to emergency exposures ranging from 10 min to 8 h. Three levels – AEGL-1, AEGL-2, and AEGL-3 – are developed for each of five exposure periods (10 min, 30 min, 1 h, 4 h, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 *is the airborne concentration (expressed as ppm [parts per million] or mg/m^3 [milligrams per cubic meter]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.*

AEGL-2 *is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.*

AEGL-3 *is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening adverse health effects or death.*

Airborne concentrations below AEGL-1 represent exposure levels that can produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, nonsensory adverse effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL." (NRC, 2004)

An overview of the AEGLs derived for HF is given in

Table 31. The 10-minute AEGL-2 was based on the absence of serious pulmonary or other adverse effects in rats during direct delivery of HF to the trachea at 950 ppm for an exposure period of 10 min (Dalbey et al., 1998; Stonybrook, 1996). The reported concentration-exposure value of 950 ppm for 10 min was adjusted by a combined AF of 10^{-3} for interspecies variation, because the rat was not the most sensitive species in other studies (but direct delivery to the trachea is a sensitive model), and an intraspecies AF of 3 to protect susceptible individuals (overall AF: 10).

Also based on the available human data, in particular Lund et al. (1997, 1999) and Largent (1960), the German MAK Commission has derived an acute 15 min peak exposure value for workers of 2 ppm (MAK Commission, 2006).

During the preparation of this report, the eMSCA assumed a human NOAEC of 2 ppm for mild irritation effects. Nevertheless, for the protection of the general population, an AF of 2 has to be assigned to account for the higher intraspecies variability as compared to the healthy probands tested in the studies by the groups of Lund and Largent (Largent, 1960; Lund et al., 1997; Lund et al., 1999).

Table 31

OVERVIEW OF AEGLS (IN PPM) SET FOR HF BY THE US NATIONAL RESEARCH COUNCIL (REPRODUCED FROM (NRC, 2004))						
Classification	**10 min**	**30 min**	**1 h**	**4 h**	**8 h**	**Endpoint (reference)**
AEGL-1 (Non-disabling)	1.0	1.0	1.0	1.0	1.0	Threshold, pulmonary inflammation in humans (Lund et al., 1997; Lund et al., 1999)
AEGL-2 (Disabling)	95	34	24	12	12	NOAEL lung effects in cannulated rats (Dalbey et al., 1998; Stonybrook, 1996)[a]; sensory irritation in dogs (Rosenholtz et al., 1963)[b]
AEGL-3 (Lethal)	170	62	44	22	22	Lethality threshold in cannulated rats (Dalbey et al., 1998; Stonybrook, 1996)[c]; lethality threshold in mice (Wohlslagel et al., 1976)[d]

[a] 10-min AEGL-2; [b] 30-min and 1-, 4-, 8-h AEGL-2 values; [c] 10-min AEGL-3; [d] 30-min and 1-, 4-, and 8-h AEGL-3 values

For evaluation of the risk of more severe tissue damage, the same PoDs are used as for the derivation of the AEGL-2. On the basis of the results of (Dalbey et al., 1998), 950 and 1589 ppm are the NOAECs for 10 or 2 min exposure.

According to the REACH IR/CSA guidance R. 8, a slightly higher overall AF of 25 (2.5 for inter- and 10 for intraspecies) is assigned as compared to the AEGL (overall AF: 10), therefore slightly lower DNELs of 64 ppm (2 min exposure) and 38 ppm (10 min) are obtained. Given the inherent uncertainties in risk characterisation, the practical relevance of these differences is low.

7.13.3. DNELs for single, acute exposure to carbonyl fluoride

The US NRC also has derived AEGLs for COF_2 based on the $BMCL_{05}$ from the acute inhalation experiment in rats (DuPont, 1976).

Table 32

OVERVIEW OF INTERIM AEGLS (IN PPM) SET FOR COF_2 BY THE US NATIONAL RESEARCH COUNCIL (REPRODUCED FROM (NRC, 2014))						
Classification	**10 min**	**30 min**	**1 h**	**4 h**	**8 h**	**End Point (Reference)**
AEGL-1 (Non-disabling)	-	-	-	-	-	Not derived due to lack of data
AEGL-2 (Disabling)	0.35	0.35	0.28	0.17	0.087	Set at one third of the AEGL-3
AEGL-3 (Lethal)	1.0	1.0	0.83	0.52	0.26	Based on the $BMCL_{05}$ from (DuPont, 1976)

In the absence of other, more substantial information about the acute toxicity of COF_2, the values listed in Table 32 are used for risk assessment. Due to lack of data, no AEGL-1 for mild effects could be derived. AEGL-2 and AEGL-3 values are significantly lower than those derived for HF, even considering that one mole of COF_2 may release two moles of HF upon hydrolysis.

7.14. Conclusions of the human health hazard assessment and related classification and labelling

The health-based reference values established for polyhaloalkene, HF, and COF_2 as an outcome of human health hazard assessment are listed in Table 33. Values for other

durations have been derived by extrapolation using Haber's law (C^n x t, for details cf. section 0).

Table 33

SUMMARY OF AVAILABLE, EXPERIMENTALLY DERIVED DNELS AND AEGLS. VALUES FOR OTHER DURATIONS HAVE BEEN DERIVED BY EXTRAPOLATION USING HABER'S LAW					
Exposure scheme	**Relevant effect**	**PoD (ppm), species value**	**Overall AF**	**Reference value (ppm)**	**Source**
Polyhaloalkene					
1 x 1 h	No acute effect	NOAEC = 100000, rabbit	25	**$DNEL_{1h}$ = 4000**	This report
1 x 6 h	No acute effect	NOAEC = 50000, rat	25	**$DNEL_{6h}$ = 2000**	This report
Chronic	Cardiac inflammation	LOAEC = 500, rabbit	2.5	**OEL = 200**	(MAK Commission, 2015)
HF					
10 min	Mild irritation	NOAEC = 1, human	1	**AEGL-1 = 1**	(NRC, 2004)
15 min	Mild irritation	NOAEC = 2, human	2	**$DNEL_{acute,mild}$ = 1**	This report
2 min	Severe effects	NOAEC = 1 589, rat	25	**$DNEL_{2\ min,severe}$ = 64**	This report
10 min	Severe effects	NOAEC = 950, rat	25	**$DNEL_{10\ min,severe}$ = 38**	This report
10 min	Severe effects	NOAEC = 950, rat	10	**AEGL-2 = 95**	(NRC, 2004)
10 min	Lethal	Mortality threshold = 1 764, rat	10	**AEGL-3 = 170**	(NRC, 2004)
COF_2					
10 min	Severe effects	$BMCL_{05}$ = 5.1, rat	15	**AEGL-2 = 0.35**	(NRC, 2014)
10 min	Lethal	$BMCL_{05}$ = 5.1, rat	5	**AEGL-3 = 1**	(NRC, 2014)

With respect to the malformations noted in the PNDT study in rabbits (WIL, 2011a), the eMSCA concludes that because these effects are only observed in rabbits, not rats, and they are linked to maternal toxicity, the currently available data do not support classification & labelling for developmental toxicity. Furthermore, these effects occurred at a comparatively high dose level and would be covered by any chronic DNEL derived in accordance with the considerations presented in section 7.13.2.2 above.

As a result, the eMSCA finds that no classification is warranted for any of the human health endpoints evaluated in this dossier.

Finally, the following assumptions in terms of hazard characterisation that were used as a starting point for the Fault Tree Analysis (FTA) in (Gradient, 2009b) are not supported:

- The DNELs assumed as relevant for the risk characterisation regarding exposure to polyhaloalkene by the Gradient study are not supported and were found by the German CA to lie substantially lower.

- The DNELs for the assessment of severe health effects as a result of exposure to HF should be set slightly lower than the AEGL-2 used by (Gradient, 2009b). On the other hand, given the uncertainties in DNEL derivation, the difference is fairly small and probably not decisive for the outcome of risk assessment.
- The assumption that persons exposed to hydrogen fluoride would feel an irresistible urge to leave the site of exposure immediately already at HF levels below those causing severe damage cannot be supported based on the results of this substance evaluation.

These assumptions affect some of the decisions made in the course of the Fault Tree Analysis (FTA), in particular for ruling out the relevance of assessing certain exposure scenarios. Therefore, as a result of these conclusions, a review of the corresponding parts of the FTA appears necessary to the eMSCA.

7.15. Assessment of endocrine disrupting (ED) properties

7.15.1. Endocrine disruption – Environment

Not assessed in the course of this evaluation.

7.15.2. Endocrine disruption - Human health

No dedicated studies on a potential of polyhaloalkene to act as an endocrine disrupter have been submitted for registration, and the REACH regulation does not contain a corresponding information requirement. However, the available data base, in particular the toxicogenomics study and the studies on pre-natal development and fertility, has produced some results which require further discussion.

As described above (section 7.9.7), the authors of the toxicogenomics study (Hamner Institute, 2008) stated in their original study report that the gene expression changes observed after treatment with polyhaloalkene were suggestive of an "endocrine-related effect".

The toxicogenomics experiment was carried out before the two-generation study in rats (TNO, 2011) was completed. In a supplement to the study report, the author wrote:

"Specifically, the organic anion transporter Slc22a7, cytochrome P-450 Cyp2c (aka Cyp2c11), prostaglandin D2 synthase (Ptgds), 15-hydroxyprostaglandin dehydrogenase (Hpgd), and ELL associated factor 2 (Eaf2) were all significantly altered by polyhaloalkene in at least one of the two dose levels […]. *Each of these genes have been shown to be regulated by androgens. However, in a separate 13 wk study* [i.e. (TNO, 2007)]*, no histopathological effects were observed in reproductive organs and a follow-up two-generation study is being performed* […] *to confirm the negative reproductive effects. Assuming that the two generation study is also negative, the interpretation of the gene expression changes observed in our study that were suggestive of endocrine-related effects would not appear to be functionally significant. As with all genomics studies, interpretation of the biological significance of the observed gene expression changes is difficult. In many cases, it is not known, what a two-fold, three-fold or even a statistically significant change in mRNA levels mean with respect to protein changes or, more importantly, on a functional level. In this case, reproductive changes consistent with alterations in circulating androgens were not evident in subsequent follow-up studies."*

These conclusions appear plausible, and therefore the eMSCA concurs with this analysis.

As described comprehensively in section 7.9.7.4, the two-generation study demonstrated treatment-related effects on biological processes that are regulated by hormones, such as gestational length and vaginal opening (VO).

7.15.3. Conclusion on endocrine disrupting properties (combined/separate)

The hormonal basis of female sexual maturation has been reviewed in great detail by (Goldman et al., 2000). In the developing female rat, a complex sequence of events must take place through post-natal weeks 1-6 before sexual maturation is achieved. This process is schematically represented in Fig. 4.

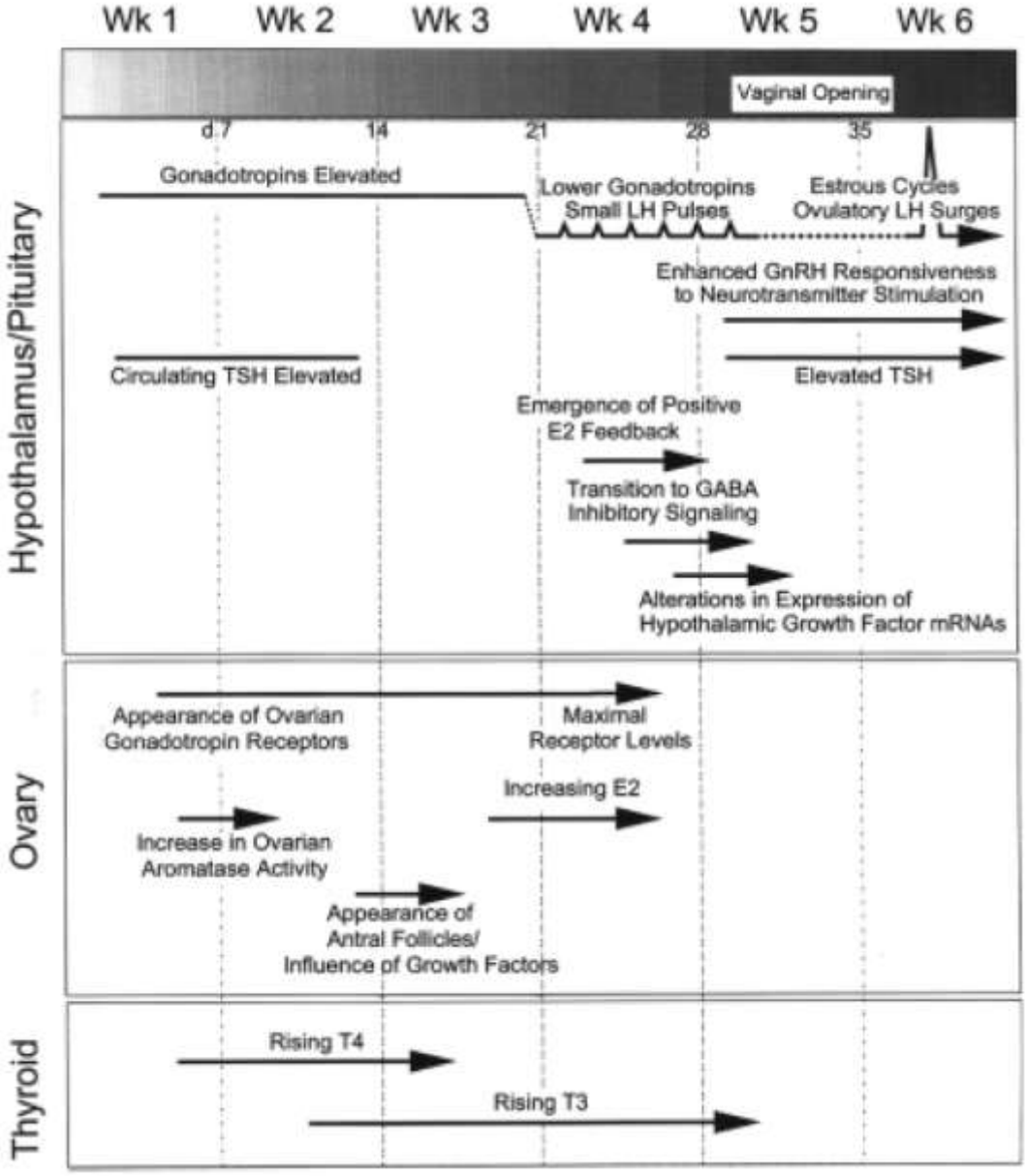


Fig. 4: Chronology of maturational changes within the female rat hypothalamus, pituitary, ovaries, and thyroid over postnatal weeks 1 through 6. The arrows indicate alterations that have been reported to commence at the times indicated (reproduced from (Goldman et al., 2000)).

The article by Goldman et al. also reviewed the knowledge on the influence of different factors, e.g. exogenous agents, on these processes. Table 34 gives an exemplary overview of effects on VO related to steroid receptor agonists or antagonists.

This might only be seen as a general orientation, and in reality, relationships are likely to be complex and not easily predicted.

On the other hand, a number of further putative/suggested mechanisms leading to a delay in VO are listed by Goldman and co-workers, e.g.

- influencing gonadotropin releasing hormone (GnRH) and luteinising hormone (LH) levels,
- interference with neurotransmitter levels,
- altered hypothalamic-pituitary regulation,
- enhancement of prostaglandin E2 levels.

Table 34

RELATIONSHIP BETWEEN STEROID RECEPTOR AGONISM/ANTAGONISM OF AN AGENT TOWARDS CERTAIN RECEPTORS AND EFFECT ON THE AGE OF MATURING RATS AT VAGINAL OPENING (GOLDMAN ET AL., 2000)		
Receptor	**Agent**	**Effect on age at vaginal opening**
Estrogen	Agonist	Decrease
	Weak agonist	Decrease
	Antagonist	Increase
Androgen	Agonist (aromatisable)	Decrease
	Antagonist	No effect

With polyhaloalkene, there is currently no further information (aside from the suggestions of the toxicogenomics report) which could elucidate the potential of polyhaloalkene to exhibit an endocrine-mediated mode of action. In principle, test batteries for endocrine active substances are available, such as e.g. the "Endocrine Disrupter Screening Program" developed by the US Environmental Protection Agency (EDSP; http://www.epa.gov/endo/pubs/edspoverview/edstac.htm), and they could probably bring more light into this matter. On the other hand, it does not appear to be justified to formally request such further information based on the current state of knowledge:

- The hypothesis for endocrine disruptive action was built on a reported association of certain gene expression changes with endocrine activity, but this association was not substantiated by a more thorough validation analysis.
- Apart from the effect on VO and perhaps a slight impact on gestation length, no other significant, generic effect on fertility was noted. In particular, no effects on reproductive organs, function, or outcome was observed in the available data base.
- A chronic DNEL derived on the basis of taking the low dose level (500 ppm) from the 28-d repeat-dose toxicity study in rabbits would be protective of the effects on VO, which occurred with significance only at 15000 ppm and above.

Finally it appears questionable whether the characterisation of polyhaloalkene as a very mildly acting endocrine disrupter would in any way substantially change the outcome of the risk assessment for this compound or lead to different regulatory consequences (rating polyhaloalkene as a priority SVHC on the basis of the observed effects seems inappropriate based on the currently available knowledge).

Therefore, the eMSCA concludes overall that the available data do not point at a relevant endocrine-disrupting activity of polyhaloalkene.

7.16. PBT and vPvB assessment

Not assessed in the scope of this evaluation.

7.17. Exposure assessment

7.17.1. Human health

7.17.1.1. Workers

As this SEv is targeted to potential risks for the general public, no risk assessment for workers and/or professionals has been carried out.

7.17.1.2. Consumers

The evaluation of human health exposures and risks was targeted to risks for the general population that may result from the use of polyhaloalkene in mobile air conditioning of passenger vehicles.

No consumer uses of polyhaloalkene have been communicated by the registrants. Moreover, direct use of the substance by consumers is advised against, including filling of mobile air conditioning units by consumers and direct/open evaporation applications. The substance is intended for use in closed air conditioning or refrigeration systems. According to the registrants, no exposure to consumers is expected under normally foreseeable conditions of use. However, releases from closed systems associated with high health risks for consumers may matter in substance evaluations under REACH. Therefore, the available information on polyhaloalkene in mobile air conditioning of vehicles is presented.

The risks associated with consumer exposure to polyhaloalkene and its thermal degradation products in the case of system failures have to be controlled on a vehicle type-specific level. Therefore, the US Environmental Protection Agency has set a condition in the final rule on polyhaloalkene use in new motor vehicle air conditioning systems for passenger cars and light-duty trucks to the effect that manufacturers must conduct Failure Mode and Effect Analyses (FMEA; (US EPA, 2011)). This condition was maintained in a further final rule on polyhaloalkene use in in newly manufactured medium-duty passenger vehicles (MDPVs), heavy-duty (HD) pickup trucks, and complete HD vans (US EPA, 2016), and the German Type Approval Authority demands compliance with the international standard ISO 13043 for passenger cars in which polyhaloalkene is used (KBA, 2011). ISO 13043 and also the international standard SAE J2773 demand Failure Mode and Effect Analyses (FMEA) or Fault Tree Analyses (FTA) for every passenger car type in which polyhaloalkene is used.

For the assessment of risks potentially arising from air conditioning systems in passenger cars, general views on probabilities for single failure scenarios have been published in risk analyses prepared by the Gradient Corporation, Seattle, USA, for the International Society of Automobile Engineers (SAE; (Gradient, 2009b; Gradient, 2013) in a Collaborative Research Program on Polyhaloalkene called SAE CRP 1234. These studies have been cited by the registrants in the CSR and include fault tree analyses (FTA) for passenger cars on a general level, while some vehicle types such as hybrid and electronic cars have been excluded from these FTAs.

As the probability of system failures highly depends on technical conditions which go far beyond the scope of operational conditions in consumer exposure scenarios under REACH, discussing the probability estimates in such vehicle type-specific risk analyses is considered beyond the scope (and possibilities) of this substance evaluation. Moreover, such studies are typically based on confidential business information from vehicle manufacturers.

Therefore, the degree of probability with which different scenarios of consumer exposure due to system failure might occur is not analysed in this consumer exposure evaluation. Instead, available information on possible consumer exposure conditions and scenarios in different cases of system failure and on associated exposure levels to polyhaloalkene and its degradation products is presented and discussed on a general level. The consumer exposure evaluation is targeted to polyhaloalkene and its degradation products, exposure to open flames and to other physico-chemical factors is not discussed here.

7.17.1.2.1. Overview of uses and exposure scenarios

7.17.1.2.1.1. Information on uses

Polyhaloalkene is used as a refrigerant in mobile air conditioning, stationary air conditioning and in refrigeration. A variety of refrigerant blends which contain polyhaloalkene can be found in the international standards on designation and safety classification of refrigerants ISO 817 and ANSI/ASHRAE Standard 34.

This evaluation considers information in registration updates submitted until 31 August 2018. It has been targeted to consumer exposure resulting from use of polyhaloalkene in AC systems of passenger cars. Consumer exposure to polyhaloalkene used in other vehicle types, e.g. in buses and coaches, as well as consumer exposure from its use in mobile refrigeration and stationary air-conditioning and refrigeration, has not been evaluated. Direct consumer use of polyhaloalkene is advised against by one or more registrants and has not been evaluated in this substance evaluation, but it has been recently registered.

7.17.1.2.1.2. Exposure scenarios

Information on consumer exposure scenarios from the latest CSR of the lead registrant can be found in the confidential annex.

The consumer exposure scenarios discussed in this evaluation report are limited to the use of polyhaloalkene in passenger cars. It should also be noted that the probability of these scenarios to occur is not discussed in this consumer exposure evaluation. It is limited to information concerning the level of exposure to polyhaloalkene and its thermal degradation products in different scenarios.

For this substance evaluation, information on exposure to polyhaloakene and its thermal degradation products is mainly based on a study cited by the registrants (Gradient, 2009b) which resulted from a cooperative research project by SAE International called CRP1234. This study differentiates several scenarios for exposure to the refrigerant itself and to hydrogen fluoride (HF) after thermal degradation of polyhaloalkene. For a scenario to occur, a combination of conditions must be met including events triggering refrigerant release (e.g. MAC system leaks), causes for thermal degradation (e.g. contact to hot surfaces, vehicle fires), locations of release, locations of exposure, and exposure of persons. The table below shows scenarios as presented in the study cited above (Gradient, 2009b), p. 36-38, Table 2-4.

After the publication of a press release on test results by the company Daimler AG, an additional risk assessment was performed in a new cooperative research project by SAE International (Gradient, 2013), and two new fault tree scenarios were added to the previous ones in order to consider individuals unable to leave the passenger cabin in the event of a vehicle fire starting in the engine compartment.

Table 35

POLYHALOALKENE HAZARD SCENARIOS CONSIDERED FOR EVALUATION VIA FTA IN CRP PHASE III - (Gradient, 2009b)								
Triggering Event	**Location of Refrigerant Release**	**Location of Potential Exposure**	**Exposed Individual**	**Type of Hazard**			**High Pressure Equipment Injury**	**Fault Tree ID**
				Refrigerant Exposure (toxicity)	**Exposure to open flame (ignition)**	**HF exposure**		
Evaporator leaks due to corrosion	Passenger compartiment	Passenger compartiment	Vehicle occupant	No evaluation via FTA. Leak is too slow, concentration will not exceed HBL.	No evaluation via FTA. Leak is too slow, concentration will not exceed LFL.	No evaluation via FTA. Leak is too slow to generate HF in significant amounts.	NA	NA
Collision	Passenger compartiment	Passenger compartiment	Vehicle occupant	No evaluation via FTA. Concentrations will not exceed HBL.	**Evaluate** via **FTA**.	**Evaluate** via **FTA**. (1)	NA	13, HF3
Collision	Engine compartment	Engine compartment	Former occupant investigating engine or good Samaritan assissting trapped occupants,	No evaluation via FTA. Concentrations will not exceed HBL.	**Evaluate** via **FTA**.	**Evaluate** via **FTA**. (2)	NA	15, HF4, HF5
Collision	Engine compartment	Passenger compartiment (aspiration from damaged engine compartment *via* air intakes)	Vehicle occupant	No evaluation via FTA. Concentrations will not exceed HBL.	No evaluation via FTA. Dilution with outside air during intake would mean LFL would not be reached.	**Evaluate** via **FTA**. (2)	NA	HF4.2
AC system leak (non-collision)	Engine compartment	Engine compartment	Former occupant investigating engine	No evaluation via FTA. Concentrations will not exceed HBL.	**Evaluate** via **FTA**.	**Evaluate** via **FTA**. (2)	NA	14, 8.2

POLYHALOALKENE HAZARD SCENARIOS CONSIDERED FOR EVALUATION VIA FTA IN CRP PHASE III - (Gradient, 2009b)								
Triggering Event	**Location of Refrigerant Release**	**Location of Potential Exposure**	**Exposed Individual**	**Type of Hazard**			**High Pressure Equipment Injury**	**Fault Tree ID**
				Refrigerant Exposure (toxicity)	**Exposure to open flame (ignition)**	**HF exposure**		
AC system leak (non-collision)	Engine compartment	Passenger compartment (via aspiration)	Vehicle occupant	No evaluation via FTA. Concentrations will not exceed HBL.	No evaluation via FTA. Dilution with outside air during intake would mean LFL would not be reached.	**Evaluate** via **FTA**. (2)	NA	HF8.1
AC system leak (non-collision)	Engine compartment	Adjacent to engine compartment	Bystander	No evaluation via FTA. Concentrations outside of engine compartment will not exceed HBL.	No evaluation via FTA. Concentrations outside of engine bay would not exceed LFL.	No evaluation via FTA. Concentrations outside of engine bay would not exceed health-based limit. Bystander will move away at low HF concentrations due to irritancy.	NA	NA
Vehicle fire due to failure of non-AC components later involves refrigerant	Engine compartment	Passenger compartment	Occupant driving vehicle with minor fire, aspiration of HF into vehicle.	NA	No evaluation via FTA. Low burning velocity of HFO-1234yf indicates minimal contribution to fire.	**Evaluate** via **FTA** (1)	NA	HF7.1
Vehicle fire due to failure of non-AC components later involves refrigerant	Engine compartment	Engine compartment	Former occupant who investigates in the engine compartment	NA	No evaluation via FTA. Low burning velocity of HFO-1234yf indicates minimal contribution to fire.	**Evaluate** via **FTA** (1)	NA	HF7.2

POLYHALOALKENE HAZARD SCENARIOS CONSIDERED FOR EVALUATION VIA FTA IN CRP PHASE III - (Gradient, 2009b)								
Triggering Event	**Location of Refrigerant Release**	**Location of Potential Exposure**	**Exposed Individual**	**Type of Hazard**			**High Pressure Equipment Injury**	**Fault Tree ID**
				Refrigerant Exposure (toxicity)	**Exposure to open flame (ignition)**	**HF exposure**		
Vehicle fire due to vandalism later involves refrigerant	Engine compartment	Engine compartment	Owner	NA	No evaluation via FTA. Low burning velocity of HFO-1234yf indicates minimal contribution to fire.	**Evaluate** via **FTA** (1)	NA	HF6
Vehicle fire related to collision, equipment failure or vandalism	Engine compartment	Engine compartment	First responder	NA	No evaluation via FTA. Low burning velocity of HFO-1234yf indicates minimal contribution to fire.	**No evaluation via FTA. HF will have dispersed by the time first responders arrive.**	NA	NA
Certified service technican	Engine compartment	Service shop	Worker	No evaluation via FTA. Concentrations in service areas will not exceed HBL.	**Evaluate** via **FTA**.	No evaluation via FTA. Workers will move away from location to avoid irritation caused by HF.	**Evaluate** via **FTA**.	16
Do-It-Yourselfer (DIY)	Engine compartment	Home garage	Owner	No evaluation via FTA. New SAE equipment service standards will mandate service by certified individuals only.				NA

NA: Hazard is not relevant to the triggering event/ exposure scenario described.

1: Generation of HF via refrigerant ignition only.

2: Generation of HF via refrigerant ignition or thermal decomposition.

For this substance evaluation, the following general exposure scenarios have been derived by the eMSCA in order to structure information on consumer exposure conditions and consumer exposure estimates from different sources:

- Scenario 1: Exposure to polyhaloalkene after a refrigerant release into the passenger cabin,
- Scenario 2: Exposure to thermal degradation products of polyhaloalkene after a refrigerant release into the passenger cabin and ignition,
- Scenario 3: Exposure to thermal degradation products of polyhaloalkene after an AC leak to the engine compartment or collision with subsequent contact of polyhaloalkene to hot surfaces, and
- Scenario 4: Exposure to thermal degradation products of polyhaloalkene in cases of vehicle fire.

Information on exposure to polyhaloalkene will be discussed under Scenario 1. In (Gradient, 2009b), exposure to polyhaloalkene was not included in the FTA because it was considered to be always below health-based limits. However, the international standards SAE J 2773 and ISO 13043 which govern the vehicle type specific risk assessments by the manufacturers demand an evaluation of polyhaloalkene releases to the passenger compartment of cars in the cases of small and large leaks of the air conditioning (AC) system. In this substance evaluation, monitoring data and modelled data for different AC leaks, cars and situations will be discussed under Scenario 1. This includes analyses of releases into the passenger compartment in the case of a collision.

It should be noted that this evaluation does not include an evaluation of direct consumer exposure to polyhaloalkene. Specifically, it does not include an exposure evaluation for recharging vehicle AC systems with polyhaloalkene by consumers.

Scenarios 2, 3, and 4 cover exposure to degradation products of polyhaloalkene. In (Gradient, 2009b), several scenarios for exposure to HF were included in the FTA. (The additional scenarios in (Gradient, 2013) did not directly cover exposure to HF). SAE J2773 demands an evaluation of exposure to hydrogen fluoride above health limits (Acute Exposure Guideline Level 2, AEGL-2) resulting from thermal degradation of refrigerant in the event of a refrigerant release. ISO 13043 demands an evaluation of degradation products (e.g. HF) above health limits (AEGL-2) resulting from refrigerant thermal degradation in the event of a refrigerant release caused by MAC system failure or a vehicle fire produced by vehicle failure.

7.17.1.2.2. Scope and type of exposure

Consumer exposure to polyhaloalkene in closed air conditioning systems of passenger cars is not foreseen under normal conditions of use. In case of accidental release of polyhaloalkene, consumer exposure is conceivable by the inhalation pathway. This exposure will be limited to the time a person spends within the car, i.e. short-term. In case of inflammation or thermal degradation of polyhaloalkene, short-term consumer exposure to its fluorinated degradation products by inhalation is conceivable. In this substance evaluation, information on exposure by inhalation to polyhaloalkene and its thermal degradation products has been evaluated.

In the following subsections, information on the level of consumer exposure to polyhaloalkene in passenger cars is evaluated for situations with AC leaks resulting from different causes. Consumer exposure to thermal degradation products of polyhaloalkene is also discussed. Consumer exposure to open flames as such is not directly discussed in this chapter, however, as combustion of polyhaloalkene may lead to exposure towards thermal degradation products, they will also be mentioned.

7.17.1.2.3. Monitoring data for polyhaloalkene

Scenario 1: Exposure to polyhaloalkene after a refrigerant release into the passenger cabin

Under normal conditions of use, no release of refrigerant from the mobile AC system is expected to occur. However, corrosion leaks in system piping occur over time. In addition, the AC system may be damaged due to failures or accidents which produce large leaks. Monitoring data provided by four Original Equipment Manufacturers (OEMs) for polyhaloalkene concentrations in passenger cabins of five different vehicles after large and very large leaks have been cited in the CRP1234 Phase III study (Gradient, 2009b):

> *"All tests involved placing a number of sensors within the vehicle, releasing the refrigerant at a set rate and evaluating the potential effects of different blower speeds and air distribution modes on the polyhaloalkene concentrations measured at different locations in the vehicle"* (Gradient, 2009b).

Table 36 summarises the concentrations provided in Gradient (2009b), p.67, Table 3-1 (cabin volumes, air change rates, refrigerant charges, blower speed and air distribution modes not cited).

Table 36

MEASURED AIR CONCENTRATIONS OF POLYHALOALKENE IN CAR PASSENGER CABINS AFTER LARGE AND VERY LARGE LEAKS. OWN REPRESENTATION BASED ON [(Gradient, 2009b), P.67]	
Leak rate, leak diameter, sampler location, number of tests	**Polyhaloalkene (ppm)**
1.14 g/s or 0.5 mm, foot area, n = 12	3000 to 108000
1.14 g/s or 0.5 mm, driver face, n = 8	< 3000 to 50200
12.4 or 13 g/s, foot area, n = 18	8000 to 147000
12.4 or 13 g/s, driver face, n = 16	0 to 50300

Evaluation

As the originals of these reports and details on sampling and analytics have not been provided, the data cannot be evaluated in detail and the time-frame for the sampling procedure is not known. However, considering the refrigerant charges and the release rates, the time-frame for release of polyhaloalkene due to large AC system leaks in passenger cars is supposed to be in the order of minutes. According to (Gradient, 2009b), a large or very large type of leak into the passenger cabin is not expected to occur by corrosion, because the refrigerant will be completely released before a leak reaches a large size.

Conclusion

For a thorough evaluation the analytical details are needed. However, considering modelling results for very large leaks, (see below) the data are plausible.

7.17.1.2.4. Modelled data for polyhaloalkene

Scenario 1: Exposure to polyhaloalkene after a refrigerant release into the passenger cabin

Leakage rates for polyhaloalkene

The following release rates have been used in the SAE CRP1234 framework in order to determine polyhaloalkene concentrations from leaks in the air conditioning system (Gradient, 2009a; Gradient, 2009b):

Table 37

MAXIMUM POLYHALOALKENE RELEASE RATES FOR DIFFERENT LEAK DIAMETERS OWN REPRESENTATION BASED ON INFORMATION IN (GRADIENT, 2009A; GRADIENT, 2009B)		
Leak type	**Leak diameter (mm)**	**Polyhaloalkene release rate (g/s)**
Small leak	0.01	0.00036
Medium leak	0.1	0.04
Large leak	0.5	1.14
Very large leak	6.5	12.4

The small, medium and large leak would correspond to corrosion processes while the very large leak would correspond to a severe line collision.

The emission time until complete release of the refrigerant is a function of the release rate. Assuming constant release at the maximum release rates, complete release of a 400 g refrigerant charge through a small leak would take more than 12 days, through a medium leak more than 2 hours, through a large leak about 6 minutes and through a very large leak 32 seconds. In reality, the pressure in the AC system will decrease with the refrigerant release and this will prolong the emission times.

Uniform Mixing modelling for polyhaloalkene concentrations from (Gradient, 2009b)

Uniform Mixing modelling has been performed in order to evaluate potential polyhaloalkene concentrations in the passenger compartment (Gradient, 2009a; Gradient, 2009b; Gradient, 2009c). Dispersion modelling was conducted for a passenger cabin size of 2.5 m^3 with an exchange rate of 1.7 air changes per hour (ACH). Because polyhaloalkene is heavier than air it was assumed that two thirds of the refrigerant charge were distributed into the lower third of the passenger compartment. In Table 38 the results of this modelling are given for the lower third of the compartment as cited in (Gradient, 2009b), p. 68, Table 3-2:

Table 38

RESULTS OF MODELLING CONDUCTED FOR POLYHALOALKENE CONCENTRATION IN LOWER 1/3 OF PASSENGER COMPARTMENT (UNIFORM MIXING MODEL) [(Gradient, 2009b), P.68]			
Conditions	**Maximum Concentration (ppm)**	**Peak 5-minute TWA (ppm)**	**Peak 30-minute TWA (ppm)**
Small diameter leak (0.01 mm), blower speed low (1.7 ACH)	16	16	16
Medium diameter leak (0.1 mm), blower speed low (1.7 ACH)	3 800	3 800	3 700
Large diameter leak (0.5 mm), blower speed low (1.7 ACH)	64 700	63500	58 400
Large diameter leak (6.5 mm orifice associated with tube rupture), blower speed low (1.7 ACH)	74 600	70 600	64 800

Evaluation

The data are plausible. As polyhaloalkene is heavier than air, they do however not represent the exposure concentration in the drivers' breathing zone.

The CRP Phase III risk assessment for polyhaloalkene relied on maximum Time Weighted Average (TWA) concentrations for 5 or 30 minutes (Gradient, 2009a). It should be noted that emission times for complete release of the refrigerant through small and very small leaks are longer and the corresponding exposure times for drivers may be longer, too.

Conclusion

The data are plausible and likely overestimate exposures after large and very large leaks. For medium and small leaks, longer exposure time periods have to be taken into consideration.

ConsExpo modelling of polyhaloalkene concentrations after small and medium AC leaks by the German CA

In order to estimate the concentrations over longer exposure times, the eMSCA performed own calculations using the ConsExpo Web tool with its constant rate model for a 'Micro Car' with an effective volume of 1.25 m³ and a refrigerant charge of 400 g:

Table 39

CONSEXPO WEB CONSTANT RATE MODELING FOR POLYHALOALKENE CONCENTRATIONS IN THE PASSENGER CABIN OF A MICRO CAR AFTER FULL RELEASE FROM SMALL AND MEDIUM AC LEAKS*				
Leak rate (g/s)	**Emission duration (min)**	**Ventilation rate (/h)**	**Polyhaloalkene time weighted average concentration (ppm)**	
			First 2h	**Peak 15 min. within first 2h**
0.03	222	2	7 100	9000
0.03	222	6	2 800	3000
0.00036	18519	2	84	110
0.00036	18519	6	34	36

* 'Micro Car' with an effective volume of 1.25 m³, refrigerant charge of 400 g, using the ConsExpo Web tool with its constant rate model.

The calculations were performed with the ConsExpo Web Version Constant rate model for leak rates of 0.03 g/s and 0.00036 g/s. A 'Micro Car' was chosen with a cabin volume of 1.25 m^3 and an applied amount of 400 g refrigerant charge. A driving time of two hours was assumed as a typical exposure time. The international standard SAE J2772 gives typical air change rates for idling vehicles as 2.0-3.0/h and for driving vehicles as 4.0-6.0/h. Thus, the ConsExpo calculations were performed with ventilation rates of 2/h and 6/h.

Evaluation

The calculations overestimate the real exposure because of several factors:

- The assumption of constant release at the maximum release rate is conservative. In reality, the pressure in the AC system will diminish over time and the release rate will fall.
- According to SAE J2772, a part of the refrigerant may remain in the engine space because it is dissolved in the lubricant.
- Polyhaloalkene will not be evenly distributed in the cabin but accumulate in the lower part, which also diminishes the concentrations in the driver´s breathing region.

Moreover, the input data of the fault tree analysis provided by the registrants assumes a probability of occurrence for medium AC leaks of 2.7^{-10} per vehicle hour based on the SAE CRP1234 Risk Assessment Phase II which was rated as very low (Gradient, 2009a).

Conclusion

The calculations give a very conservative estimate for polyhaloalkene exposure from small and medium AC leaks.

CSR information on consumer exposure to polyhaloalkene after a collision

See confidential annex for details.

7.17.1.2.5. Comparison of monitoring and modelled data for polyhaloalkene

Scenario 1: Exposure to polyhaloalkene after a refrigerant release into the passenger cabin

Only modelled data are available for exposure to polyhaloalkene from small and medium AC leaks.

For exposure in the driver´s breathing zone after a full release from large or very large leaks, the measured data from the CRP1234 framework (Gradient, 2009b) can be compared to the modelling data for collisions from the registrations (see confidential annex).

For exposure in the lower part of the vehicle cabin after a full release from large or very large leaks, modelled as well as monitoring data are available. Consistency between these data is quite good if the different conditions in vehicles and the model assumptions are considered.

It should be noted that monitoring and modelling results are highly dependent on sampling and/or exposure time. While for large and very large leaks the maximum concentration will be reached after seconds to minutes, it will only be reached after hours in the case of small and very small leaks. Table 40 summarises the presented monitored and modelled concentrations of polyhaloalkene for different leak diameters and exposure times.

Table 402

MODELLED AND MONITORED POLYHALOALKENE CONCENTRATIONS IN THE CABIN AFTER AC LEAKS OF DIFFERENT SIZES Conditions	Exposure time	Avg. conc. of polyhaloalkene (ppm)	Source
Small leaks			
Modelled concentration in lower part of passenger compartment, 0.01 mm leak, blower speed low, 1.7 ACH, 2. 5 m³	5 min	16	(Gradient, 2009b)
ConsExpo constant rate modelling for 400 g charge, 1.25 m³ 6 ACH, leak rate 0.00036 g/s for 0.01mm leak	15 min	36	This report
ConsExpo constant rate modelling for 400 g charge, 1.25 m³, 2 ACH, leak rate 0.00036 g/s for 0.01 mm leak	15 min	110	This report
Modelled concentration in lower part of passenger compartment 0.01 mm leak, blower speed low, 1.7 ACH, 2.5 m³	30 min	16	(Gradient, 2009b)
ConsExpo constant rate modelling for 400 g charge, 1.25 m³,6 ACH, leakage rate 0.00036 g/s for 0.01 mm leak	2h	34	This report
ConsExpo constant rate modelling for 400 g charge, 1.25 m³,2 ACH, leakage rate 0.00036 g/s for 0.01 mm leak	2h	84	This report
Medium-sized leaks			
Modelled concentration in lower part of passenger compartment, 0.1 mm leak, blower speed low, 1.7 ACH, 2.5 m³	5 min	3800	(Gradient, 2009b)
ConsExpo constant rate modelling for 400 g charge, 1.25 m³, 6 ACH, leak rate 0.03 g/s for 0.1 mm leak	15 min	3000	This report
ConsExpo constant rate modelling for 400 g charge, 1.25 m³ 2 ACH, leak rate 0. 03 g/s for 0.1mm leak	15 min	9000	This report
Modelled concentration in lower part of passenger compartment 0.1 mm leak, blower speed low, 1.7 ACH, 2.5 m³	30 min	3700	(Gradient, 2009b)

MODELLED AND MONITORED POLYHALOALKENE CONCENTRATIONS IN THE CABIN AFTER AC LEAKS OF DIFFERENT SIZES Conditions	Exposure time	Avg. conc. of polyhaloalkene (ppm)	Source
ConsExpo constant rate modelling for 400 g charge, 1.25 m³, 6 ACH, leakage rate 0.03 g/s for 0.1mm leak	2 h	2800	This report
ConsExpo constant rate modelling for 400 g charge, 1.25 m³, 2 ACH, leakage rate 0.03 g/s for 0.1mm leak	2 h	7100	This report
Large and very large leaks			
Analyses from 24 samples near drivers´ face after refrigerant release into passenger cabin, different vehicles and air modes, leak rates 1.14, 12.4, or 13 g/s, sampling time not given	5 min	0-50300	(Gradient, 2009b)
Modelled concentration in lower part of passenger compartment, 0.5 mm leak, blower speed low, 1.7 ACH, 2.5 m³	5 min	63500	(Gradient, 2009b)
Modelled concentration in lower part of passenger compartment, 6.35 mm, blower speed low, 1.7 ACH, 2.5 m³	5 min	70600	(Gradient, 2009b)
ConsExpo constant rate modelling for collision scenarios	Cf. additional information in confidential annex		
Modelled concentration in lower part of passenger compartment 0.5 mm leak, blower speed low, 1.7 ACH, 2.5 m³	30 min	58400	(Gradient, 2009b)
Modelled concentration in lower part of passenger compartment, 6.35 mm leak, blower speed low, 1.7 ACH, 2.5 m³	30 min	64800	(Gradient, 2009b)

The confidential annex contains information on calculations from the registration.

7.17.1.2.6. Scenarios 2, 3, and 4: Formation of carbonyl fluoride (COF_2) and hydrogen fluoride (HF) after combustion of polyhaloalkene

According to a study on safety issues in the application of flammable refrigerant gas in MAC, the combustion of one mole of polyhaloalkene with a stoichiometric amount of oxygen will produce two moles of hydrogen fluoride (HF) and one mole of carbonyl fluoride (COF_2) (Monforte and Caretto, 2009). Although designated by the authors as a "key intermediate" the latter has however not been further considered in their analysis, perhaps because the authors assumed that it hydrolyses immediately, producing two further moles of HF.

(Gradient, 2009a) notes that *"the products of the decomposition of hydrofluorocarbons include HF, CO_2, carbon monoxide (CO) and carbonyl fluoride (COF_2). Carbonyl fluoride readily converts in the presence of moisture to CO_2 and HF"*, however the hypothesis of "ready conversion" is neither explained in further detail, nor supported by any reference. According to (Gradient, 2009b), *"for fluorocarbon refrigerants, exposure to a sufficient energy source may lead to either refrigerant ignition/combustion or thermal decomposition. In such cases, refrigerants like R-134a and HFO-l234yf will produce hydrogen fluoride (HF), carbonyl fluoride (COF2) as well as other very short lives intermediates. The potential for production of fluorinated breakdown products from fluorinated refrigerants is a well known property that has been studied due to the use of these chemicals as flame suppression agents. [...] Initial testing [...] indicated that the concentrations of HF produced by combustion of HFO-1234yf were not significantly different from those produced by R-134a (Honeywell, March 24, 2008). However, these tests were carried out with HFO-l234yf concentrations of 4% or less and CRP1234 members agreed that higher HFO-1234yf concentrations and HF levels could potentially occur in the event of a large release which might be associated with events such as a serious collision or car fire. Evaluating potential HF exposures was therefore a major focus of the Phase lll risk assessment and both bench scale tests (conducted primarily at INERIS) and field tests (conducted by Hughes Associates) were conducted to better understand this possible*

hazard". In the additional risk assessment reported in (Gradient, 2013), COF_2 is not addressed.

Although this is not explicitly stated, the eMSCA concludes that for the vehicle-related risk assessments reported in the Gradient studies, the authors assumed that any COF_2 formed as an intermediate would hydrolyse so rapidly that only HF would be the relevant agent to be considered for human risk assessment after exposure to the thermal degradation products of polyhaloalkene.

However, no actual proof was provided to support this assumption. Moreover, while the eMSCA agrees that immediate hydrolysis to CO and HF is likely when COF_2 gas is led through water (such as in (Hughes, 2009a; Hughes, 2009b), cf. below), it is not immediately obvious why the same should apply when COF_2 merely comes into contact with the moisture contained in ambient air. In fact, if COF_2 would immediately decompose to (2 moles of) HF, the observed considerably higher relative toxicity of COF_2 vs. HF could not be explained. Rather, this observation seems to imply that some COF_2 will remain intact – at least for a limited time – even after contact with moist body tissue in the lung, and exert addditional toxicity either on its own or e.g. maybe by allowing for the ultimate toxic action of HF to take effect in deeper airway compartments than after direct HF exposure.

When testing for potential toxic by-products originating from the application of hydrofluorocarbon (HFC)-based fire suppression systems, (Miser et al., 1998) found measurable COF_2 concentrations for between two and five minutes after the extinguishing event, depending on the HFC used.

In 2014, Kornath and co-workers (Feller et al., 2014) reported combustion experiments with different polyhaloalkene/oxygen mixtures and were able to qualitatively demonstrate the formation of CO_2, COF_2, and HF as typical combustion products by FT-IR analysis. Although the authors did not attempt quantification, the obtained IR spectra show that more COF_2 was formed when oxygen was supplied in a stoichiometric amount (molar ratio O_2:polyhaloalkene = 2.5:1) than in an experiment with a molar ratio O_2:polyhaloalkene of 1:2.

The authors also pointed out that COF_2 formation is unique to unsaturated HFCs. In addition, they noted that *"to our knowledge risk assessment studies for HFO-1234yf only consider the formation of HF. If COF_2 is mentioned as a potential combustion product, it is assumed that it undergoes a rapid hydrolysis with formation of CO_2 and HF. Therefore it is claimed to be irrelevant for safety issues. To our knowledge the hydrolysis kinetics of COF_2 have not been investigated yet, but from laboratory practice it is known that COF_2 does not undergo an immediate hydrolysis under contact with water"* (Feller et al., 2014). Since the main focus of this publication was on the crystallographic structural elucidation of polyhaloalkene, only few experimental details are given regarding the combustion experiments. For example origin and purity of the test material, the detailed experimental setup (e.g. volume of or pressure and temperature within the reaction vessel before ignition) for the combustion experiment, temperature of the wire used for ignition, humidity (important for COF_2 hydrolysis) are all not reported, no reference IR spectrum for COF_2 is provided, the absolute concentrations of the combustion products are not given, HF apparently is spectrometrically deteremined indirectly after reaction with the reaction vessel, but corresponding reactions as well as other possible ways of decomposition are not discussed for COF_2, figures of merit of the analytical methods are not provided and editorial review apparently was flawed, too.

As a consequence, the study only allows for very limited conclusions on the formation of COF_2 in real-life leakage/accident situations. In particular, no concentration-time profile of COF_2 is provided for the different experiments. Nevertheless, the eMSCA takes the results as a qualitative indication that clearly measurable amounts of COF_2 are generated in the event of polyhaloalkene combustion.

In a series of combustion experiments with commercial polyhaloalkene (DuPont™ Opteon® YF) mixed in various ratios with air, a total of 25 chemical species (including unburned parent substance) were identified in the combustion gas (Magnusson et al., 2016). Depending on the polyhaloalkene:air ratio employed, the four most prominent substances

showed "emission factors" of 220-480 mg (unconsumed 2,3,3,3-tetrafluoroprop-1-ene), 170-360 mg (COF_2), 120-320 mg (CO_2), and 70-240 mg (HF) per g Opteon$^{(R)}$ YF. Arguably, the amount of COF_2 could have been overestimated because dried, filtered air was used for combustion, thereby reducing the opportunity for hydrolysation. As also reporting of experimental details is rather scarce (details on the results of the individual experiments are not reported, sampling times are not provided, concentration-time profiles are not provided etc.) no further conclusions can be drawn regarding real formation of COF_2 in real-life scenarios involving combustion of polyhaloalkene. However, the eMSCA shares the view of the authors that *"since the combustion conditions (specifically temperature and oxygen availability) in the case of a real fire diverges, the results from this controlled laboratory small-scale combustion experiment in terms of formed combustion products and their relative amounts must thus be regarded as indicative"* (Magnusson et al., 2016) but takes the results as further proof that COF_2 should be accounted for as a relevant component of combustion gases resulting from the combustion of polyhaloalkene.

Another publication on the molecular dynamics simulation of the thermal decomposition of polyhaloalkene offered interesting insights into the mechanisms and early processes in polyhaloalkene combustion. However, it cannot be used to draw conclusions on the concentrations of polyhaloalkene thermal degradation products in real-life vehicle leakage or accident scenarios (Cao et al., 2017).

Conclusion

Based on the above findings, the eMSCA concludes that in the event of thermal degradation of polyhaloalkene, COF_2 may be formed in significant - albeit not exactly known – quantities. Furthermore, in such events, relevant COF_2 concentrations could be measured for several minutes, which clearly disproves the assumption of the registrants following which by contact with moisture of the ambient air any generated COF_2 would immediately hydrolyse to CO and HF and therefore not have to be taken into account for further risk assessment.

On the contrary the eMSCA further concludes that individuals may be exposed to COF_2 for several minutes following an accidental release of polyhaloalkene onto sufficiently hot surfaces or into open flames.

Finally, as a consequence of these considerations the eMSCA concludes that – given the higher relative toxicity of COF_2 vs. HF - any risk assessment regarding exposure scenarios involving thermal degradation products of polyhaloalkene is likely to underestimate the ensuing risk if only HF toxicity is considered. Or, in the words of (Feller et al., 2014): *"Since the toxicity of COF_2 is much larger than that of HF, and our studies have shown that COF_2 is formed as one major combustion product, it should be considered in safety risk analyses"*.

7.17.1.2.7. Monitoring data for thermal degradation products of polyhaloalkene

Scenario 2: Exposure to thermal degradation products of polyhaloalkene after a refrigerant release into the passenger cabin and subsequent ignition

Field study by (Hughes, 2009b)

(Hughes, 2009b) released a typical refrigerant charge via the AC ducts into a standard mid-size passenger cabin (2.77 m³). The pressure relief valves were sealed and the AC blower was operated in order to ensure a high concentration in the driver`s breathing zone. When the concentration reached its maximum, ignition by means of a butane lighter was attempted. At higher concentrations of polyhaloalkene this was not possible and an additional spark was used in order to ignite the refrigerant-air mixture. The air was collected by sampling pumps near the driver`s breathing zone for time-frames from 3 minutes to 30 minutes and drawn through collection fluid which was later analysed for its fluoride ion content using a fluoride ion-sensitive electrode. Therefore the results also may include other fluoride species (e.g. COF_2). Nevertheless, they were calculated as HF concentrations.

Table 41 and

Table 424 show results of these experiments (see also (Gradient, 2009b), p.70, Table 3-5).

Table 41

HF CONCENTRATIONS IN A PASSENGER CABIN AFTER IGNITION OF POLYHALOALKENE WITH A BUTANE LIGHTER (HUGHES, 2009B) OWN REPRESENTATION BASED ON CITATION IN (Gradient, 2009b)			
Test	**Condition**	**Polyhaloalkene at ignition (ppm)**	**HF (ppm), 0-3 min**
SAE8	Slow discharge	1 900	0.64
SAE5	Quick discharge	7 100	1.86
SAE6	Quick discharge	9 000	1.28
SAE11	Quick discharge	10 300	4.06
SAE4	Quick discharge	10 800	5.42
SAE7	Quick discharge	13 000	1.59
SAE9	Slow discharge	19 600	3.10
SAE10	Slow discharge	36 000	5.08

Table 42

HF CONCENTRATIONS IN A PASSENGER CABIN AFTER IGNITION OF POLYHALOALKENE WITH A SPARK AUGMENTED BUTANE LIGHTER (HUGHES 2009B) OWN REPRESENTATION BASED ON CITATION IN (Gradient, 2009b)			
Test	**Condition**	**Polyhaloalkene at ignition (ppm)**	**HF (ppm), 0-3 min**
SAE14	Spark-augmented quick discharge	26 000	10.3
SAE12	Spark-augmented quick discharge	32 000	14.3
SAE16	Spark-augmented quick discharge	33 000	13.6
SAE13	Spark-augmented quick discharge	35 000	21.2
SAE19	Spark augmented quick discharge	40 000	23.5
SAE18	Spark augmented quick discharge	42 000	11.9
SAE20	Spark augmented quick discharge	42 000	34.5

Evaluation

The experiments were conducted in order to analyse a possible association of different concentrations of polyhaloalkene and the resulting concentration of HF in the case of ignition by a butane lighter. The highest tested concentration of polyhaloalkene was 4.2% while in monitoring experiments by OEMs up to 5.3% had been reached in the driver´s breathing zone.

Conclusion

The data are well documented and plausible. Due to the analytical method, the HF results also may include other fluoride species (e.g. COF_2).

Scenario 3: Exposure to thermal degradation products of polyhaloalkene after an AC leak to the engine compartment or collision and contact of polyhaloalkene with hot surfaces

HF generated in the engine space may also affect vehicle occupants if it is transported to the passenger cabin or if former vehicle occupants open the hood to check the engine. Contact of polyhaloalkene with hot surfaces in the engine compartment is a possible source of degradation products.

Field study by (Hughes, 2009a)

A field study was performed by (Hughes, 2009a) who released 575 g polyhaloalkene in combination with 3% polyalkylene glycol (PAG) oil with a release rate of 12 g/s in the direction of an artificial "hot body" (stainless steel pipe, 36.8 cm length, 6.3 cm diameter, 450 °C and 700 °C) in a distance of 5 cm in the engine space of a Cadillac CTS. Movement of gases from the engine compartment to the passenger compartment is normally blocked by the hood and its seals. However, in a collision event the hood and seals may be damaged. Therefore, the experiments were performed with the hood open, closed, or partially open in order to simulate this situation. Gas samples were taken in the breathing zone of vehicle occupants, below and above the hot surface and in three other standard positions, drawn through collection fluid and later analysed with a ion-sensitive electrode. Consequently, the results also may include other fluoride species (e.g. COF_2). Nevertheless, they were calculated as HF concentrations. Table 43 shows the concentrations of polyhaloalkene and HF determined in these experiments as cited in Table 3-6 in (Gradient, 2009b), p.71.

Table 43

RESULTS OF ENGINE COMPARTMENT HF CONCENTRATION MEASUREMENTS OBTAINED BY (HUGHES, 2009A). OWN REPRESENTATION BASED ON CITATION IN (Gradient, 2009b)

Test	Hot body temperature (°C)	Hood position and fan setting	HF in air (ppm), engine compartment§	HF in air (ppm), passenger compartment, driver's breathing zone#	Deposition sample conc. (µg/cm²)
Test1U	450	Open/on	4.3 / 7.5	2.8	N/A
Test2U	450	Closed*/on	0.4 /0.6	0.4	N/A
Test3U	700	Mid-way/on	0.9 /0.1	0.8	0.01-0.04
Test4U	700	Closed*/on	81.8 / 118.8	49.6	0.01-46.8
Test7U$	700	Closed*/off	47.3 / 80.4	2.3	0.07-25.2
Test9U$	700**	Closed*/on	7.8-53.3	12.0	0.08-0.24

Polyhaloalkene refrigerant charge: 575g. * In these tests the engine compartment seals were intentionally compromised. ** In this test the refrigerant was not discharged directly onto the hot surface, but from a distance of approximately 12.5 inches away; § First number indicated the HF concentration measured in the engine compartment below the hot surface, the second number is the concentration measured above the hot surface. $ Tests conducted by Hughes Associates under contract to GM and Ford Motor Company. Results were provided to CRP1234. # Tests were conducted with the AC fan running to evaluate whether HF generated in the engine compartment will be aspirated into the passenger compartment through the air intake vents located beneath the windshield.

In addition, a Fourier transform infrared spectrometer (FT-IR) was used to monitor HF concentrations along the side of the car. This device did not detect HF concentrations above the detection limit of "*approximately 90 ppm*" (Gradient, 2009b).

Evaluation

These values illustrate that in case of contact of polyhaloalkene with hot surfaces under field conditions, vehicle occupants and persons opening the hood may be exposed to thermal degradation products of polyhaloalkene. Many of the experimental conditions represent worst case situations (full discharge, location of hot body, different hood positions) but others may not (cabin volume, air flows inside and outside the car, relation

of emission time to sampling time). In the experiments by Hughes only one out of four tests produced an open flame. This setting produced the maximum concentrations of HF in the test series.

Conclusion

The data are well documented and plausible. However, the resulting concentrations of HF may not reflect the maximum possible HF concentrations if polyhaloalkene comes in contact to hot surfaces in the engine compartment. Due to the analytical method, the HF results also may include carbonyl fluoride (COF_2) and other fluoride species.

Experiments by the Daimler AG and by the German Kraftfahrt-Bundesamt

In September 2012, the company Daimler AG communicated the results of experiments in which polyhaloalkene was dynamically dispersed at high pressure near to hot components of the test vehicle's exhaust system. According to Daimler, "*this corresponds to a serious head-on collision in which the refrigerant line is severed and the reproducible results demonstrate that the refrigerant, which is otherwise difficult to ignite under laboratory conditions, can indeed prove to be flammable in a hot engine compartment"* (Daimler, 2012)

In order to clarify whether these experiments corresponded to risks that would require immediate risk management according to the General Product Safety Directive (Directive 2001/95/EC), the German Federal Motor Transport Authority (Kraftfahrt-Bundesamt, KBA) conducted own experiments with four cars that were available on the market in 2013. These experiments were targeted to clarify whether *"a fire could break out in a vehicle with a hot engine after a refrigerant leakage occurred."* The trials by KBA had a different setting than the Daimler trials because their main aim was to clarify the need for immediate action according to product safety law. In the following paragraphs, the tests are summarised as described in the KBA report and in his annexes (KBA, 2013).

One of each of the four vehicle types with the highest number of registrations with type approvals for the refrigerant R-1234yf was selected. In a first test phase, the maximum temperatures of components in the engine compartment under driving conditions were determined. Then, the vehicles were crashed in a realistic test set-up comparable to ECE regulation 94 with an impact speed of 40 km/h. Subsequently, their refrigerant-containing components were checked for damage. In a second test phase, separate leakage tests were performed with refrigerant in vehicles with hot engines (maximum temperature-50 °C) simulating the damage resulting from the crash tests in order to check for the development of fire and hydrogen fluoride. These leakage tests were varied according to three test levels:

"In the level 1 tests, the refrigerant was released only through the components which leaked as a result of the crash damage. Level 2 also subjected components to the release test that had been damaged in the crash test but had not leaked, but which are known – and have been shown in manufacturers' own tests – to have leaked after damage in similar tests, although there is scattering of the results due to component tolerances, etc. Level 3 is intended to confirm the findings. This level considers damage to system components which are assumed to remain leakproof in the given crash parameters if in new condition but in more severe conditions, such as ageing of the tubing material and/or higher collision speed, are likely to be destroyed. In addition, it assumes higher temperatures in the engine compartment on the basis of expected developments in engine technology, such as the use of supercharged engines in the test vehicles, which in this test were fitted with a naturally aspirated engine. The test conditions at level 3 allowed an assessment to be made from the test result of the potential for serious accidents, without determining their probability or significance. They indicate a need for further testing.

On the basis of the above, levels 1 and 2 can be used to make an official assessment of potential risk within the statutory remit of the product safety authority (assessment of a specific product). By contrast, level 3 is in the nature of a more general risk assessment. The aim is to test whether the current safety requirements are sufficient." (KBA, 2013)

Hydrogen fluoride (HF) concentrations in the engine compartment were determined during the leakage tests by means of the LaserGas III, a portable diode laser spectrometer by Bernt Messtechnik GmbH. In addition, Dräger hand pumps were used in the engine compartment and an automatic Dräger pump in the cockpit, both fitted with Dräger test tubes.

No ignition or HF release was observed in the level 1 and level 2 tests. The level 3 experiments produced an ignition in one of the four vehicles which was confirmed in one of two repeating tests under the same conditions. For safety reasons, the measurement technicians were moved back from the vehicle upon detection of ignition, the measuring probe of the LaserGas III was removed from the engine compartment at the same time and the flames were extinguished at least 10 seconds after detection of ignition. Nevertheless, the LaserGas III determined peak HF concentrations of 5364.98 ppm and 3254.22 ppm in the engine compartment. These peaks were detected at about 40 to 60 seconds after the start of the tests.

In two other level 3 experiments, without ignition, HF peak concentrations of 150.41 ppm and 133.20 ppm were detected in the engine bay. The concentrations were above the AEGL-2 value of 95 ppm for less than 30 seconds.

Evaluation

The analyses were targeted to HF and do not give any information on COF2 and other fluoride species that might have been produced. They were based on continuous monitoring that avoids averaging over the sampling time and is able to detect very short and high peak concentrations. It is noted that the measuring device was designed for concentrations up to 200 ppm and that the higher values are uncertain.

The hydrogen fluoride released into the engine bay will be diluted to an unknown extent as it spreads from the engine compartment. Accordingly, the HF concentration that individuals in the vicinity of the engine compartment might inhale will be lower, to an unknown extent, than the measured values.

HF was not detected in the interior of the vehicle in any of the tests. However, the tests were stopped upon detection of ignition. Higher HF releases into the engine compartment and spread of HF to the cabin and/or alongside the vehicle cannot be excluded in the case of a more prolonged fire -As the peak HF concentrations were reached within seconds, it is doubtful whether bystanders would be able to move away before inhaling relevant amounts of HF in such a situation.

The KBA performed an evaluation of its test results (KBA, 2013). As no ignition had occurred in the level 1 and level 2 tests, no need for an immediate intervention according to product safety law was seen. However, due to the ignitions seen under unfavourable conditions in the level 3 tests, the KBA saw the need to clarify the conditions of inflammation and HF generation and strongly recommended further investigations.

The European Commission Directorate-General Joint Research Centre performed an additional evaluation of the tests performed by the KBA (JRC, 2014a; JRC, 2014b).. This evaluation was also based on a consultation with stakeholders. It mainly discussed the test design conditions and their probability of occurrence in reality. The probability of the level 3 scenarios that lead to an ignition with HF generation was considered too low to justify immediate interventions according to product safety law. In contrast to the KBA recommendations in their report (KBA 2013) and in the consultation, no further research was recommended by the JRC.

Conclusion

The tests performed by KBA in the context of their function as product safety authority and their analysis are well-documented and plausible. In contrast to the experiments by (Hughes, 2009a), the experiments by (KBA, 2013) show that in the event of an ignition of polyhaloalkene on a hot surface in the engine bay the concentrations of HF that can be produced in the engine compartment within seconds are high. Spreading of the thermal degradation products to the cabin and exposure of vehicle occupants as well as spreading alongside the vehicle and exposure of bystanders have to be considered in such a situation

(Hohenstein and Kornath, 2012; Hughes, 2009a; Hughes, 2009b; Kornath et al., 2012; Miser et al., 1998).

7.17.1.2.8. Modelled data for thermal degradation products of polyhaloalkene

Scenario 4: Exposure to thermal degradation products of polyhaloalkene in cases of vehicle fire

No quantitative modelling has been found for this situation. In a theoretical scenario the refrigerant would be completely combusted by vehicle fire, e.g. after a frontal collision of a 'Micro Car'. It cannot be ruled out that 'Good Samaritans' will try and rescue persons in the vehicle before trained first responders arrive. Some of them may ignore irritation symptoms by HF in order to save lives. Therefore, some considerations are made on the potential distribution of HF in the car surroundings: 400 g refrigerant charge would be combusted in the engine bay of a 'Micro Car' producing up to 280 g HF. Equally distributed into a space of 10 m³ around the engine, this mass would produce an air concentration of 28000 mg/m³ or about 34 244 ppm.

Exposure of passengers in the car is conceivable as well. If only 1% of the 280 g HF, i.e. 2.8 g HF, were released into the passenger cabin volume of 1.25 m³ by aspiration of air or by dispersion of air through damaged hood seals and windows, this would correspond to a maximum HF concentration of 2240 mg/m³ or 2740 ppm.

These considerations are quite simple, because they ignore the influence of air flows, dilution and surroundings, and they are overconservative because they assume complete combustion. Nevertheless, the calculations illustrate that the upper margin of HF exposure in the case of a vehicle fire is high.

7.17.1.2.9. Comparison of monitoring and modelled data for thermal degradation products of polyhaloalkene

In (Gradient, 2009b), different scenarios for exposure to hydrogen fluoride (HF) after thermal degradation of polyhaloalkene have been discriminated (see (Gradient, 2009b), Tables 2-4). The scenarios consist of combinations of conditions which have to combine for the scenario to occur. These scenario conditions include triggering events for refrigerant release (MAC system failure or vehicle fire), causes of thermal degradation (ignition, contact with hot surfaces, vehicle fires), locations of release and exposure, and exposed individuals. All scenarios considered to be associated with a potential inhalation exposure to HF above the 10 minute AEGL-2 value of 95 ppm were included into a fault tree analysis in order to analyse their probability. It should be noted that the Derived No Effect Level (DNEL) derived for this substance evaluation in the present report is slightly lower, cf. section 0.

Below, monitoring and modelling results with respect to potential exposure to HF are evaluated together with the estimates on the possibility of HF exposure above 95 ppm for different situations given in (Gradient, 2009b). The information is structured by Scenarios 2, 3, and 4 of this consumer exposure evaluation:

Scenario 2: Exposure to thermal degradation products of polyhaloalkene after a refrigerant release into the passenger cabin and ignition

No modelling data are available for this scenario. It has been addressed in the experimental monitoring designs by (Hughes, 2009b) for ignition by a butane lighter which gave a maximum HF concentration of 34.5 ppm. The maximum concentration of polyhaloalkene in these experiments was 4.2%, while higher concentrations had been monitored by OEMs. Therefore somehow higher HF concentrations are conceivable in cases of refrigerant release into the passenger cabin and it has been included into the fault tree analysis by (Gradient, 2009a) for the case of a collision. In contrast, the non-collision-induced AC leak was not included because polyhaloalkene was assumed to evaporate slowly without reaching the lower flammability limit.

The table below summarises the assessment in Gradient (2009b) regarding the possibility of HF exposure above 95 ppm in these situations.

Table 44

EXPOSURE OF VEHICLE OCCUPANTS TO HF AFTER AN AC LEAK TO THE PASSENGER CABIN OR COLLISION AND IGNITION. OWN REPRESENTATION BASED ON (Gradient, 2009b)				
Triggering event	**Location of release**	**Location of exposure**	**Exposed Individual**	**HF > 95 ppm**
Collision	Passenger compartment	Passenger compartment	Vehicle occupant	Yes, FTA Scenario HF3
Evaporator leaks due to corrosion	Passenger compartment	Passenger compartment	Vehicle occupant	No

Evaluation and conclusion

The inclusion of collision leaks in the FTA and the argumentation that polyhaloalkene would evaporate slowly without reaching the lower flammability limit in case of corrosion leaks are plausible.

Scenario 3: Exposure to thermal degradation products of polyhaloalkene after an AC leak to the engine compartment or collision and contact of polyhaloalkene with hot surfaces

The assessments in (Gradient, 2009b) regarding the possibility of HF exposure above 95 ppm under these conditions are summarised in Table 45. Scenarios which concern exposure of bystanders who are able to leave the scene of the accident were not included in the fault tree analysis due to the corrosive properties of HF. In addition, (Gradient, 2009b) assumes that concentrations outside the engine bay would not exceed 95 ppm.

Table 45

EXPOSURE TO HF AFTER AN AC LEAK TO THE ENGINE COMPARTMENT OR COLLISION AND CONTACT OF POLYHALOALKENE TO HOT SURFACES. OWN REPRESENTATION BASED ON (GRADIENT, 2009B)				
Triggering event	**Location of release**	**Location of exposure**	**Exposed Individual**	**HF > 95 pm**
Collision	Engine compartment	Passenger compartment (aspiration from engine compartment)	Vehicle occupant	Yes, FTA Scenario HF4.2
Collision	Engine compartment	Engine compartment	Former occupant or 'good Samaritan' assisting trapped occupants	Yes, FTA Scenario HF4, HF5
AC leak (non-collision)	Engine compartment	Passenger compartment (aspiration from engine compartment)	Vehicle occupant	Yes, FTA Scenario HF8.1
AC leak (non-collision)	Engine compartment	Engine compartment	Former occupant	Yes, FTA Scenario HF 8.2
AC leak (non-collision)	Engine compartment	Adjacent engine	Bystander	No

Evaluation

The evaluations and conclusions for monitoring data in section 7.17.1.2.7 explain why the data by (Hughes, 2009a; Hughes, 2009b) do not provide sufficient proof to exclude higher HF concentrations and why the argumentation that HF concentrations outside the engine bay will not exceed 95 ppm is not supported by the measured data from (KBA, 2013). In

addition, the FTA by (Gradient, 2009b) did not consider exposure to COF_2 which can be formed in all scenarios where polyhaloalkene is thermally degraded.

Conclusion

The estimation that the above-mentioned scenarios may produce HF exposures above 95 ppm is supported. However, the argumentation that HF concentrations outside the engine bay will not exceed 95 ppm in the case of contact of polyhaloalkene to hot surfaces is not supported. Exposure of bystanders to HF above 95 ppm cannot be excluded in case of an ignition. Exposure to COF_2 should be additionally considered in all scenarios with thermal degradation of polyhaloalkene.

Scenario 4: Exposure to thermal degradation products of polyhaloalkene in cases of vehicle fire

The fault tree analysis by (Gradient, 2009b) has included three situations with potential exposures to HF over 95 ppm associated with a fire in the engine compartment. These situations are summarised in Table 58:

Table 468

EXPOSURE TO HF IN CASES OF VEHICLE FIRES. OWN REPRESENTATION BASED ON (GRADIENT, 2009B)				
Triggering event	**Location of release**	**Location of exposure**	**Exposed Individual**	**HF > 95 ppm**
Vehicle fire (vandalism)	Engine compartment	Adjacent engine	Owner	Yes, FTA Scenario HF 6
Vehicle fire (non-AC)	Engine compartment	Passenger compartment (aspiration from engine compartment)	Vehicle occupant	Yes, FTA Scenario HF 7.1
Vehicle fire (non-AC)	Engine compartment	Engine compartment	Former occupant	Yes, FTA Scenario HF 7.2
Vehicle fire (all)	Engine compartment	Engine compartment	First responder	No

First responders are supposed to arrive when HF is already dispersed. The exposure of bystanders in the case of vehicle fires is not discussed.

In addition, the fault tree analysis does not consider increased hazards from thermal degradation products of polyhaloalkene in confined spaces such as tunnels and garages which may result from refrigerant releases or vehicle fires. According to (Gradient, 2009b), p.32,

> *'Tunnels and similar structures (e.g. underground parking garages) are designed with ventilation systems to remove carbon monoxide and other combustion byproducts and such systems should be capable of rapidly diluting the HF generated from the release of refrigerant in a single vehicle to below health limits. In the case of a vehicle fire in a tunnel (including a fire involving multiple vehicles) the HF (which is lighter than air) would rise towards the roof of the tunnel.'*

Evaluation

See also evaluation and conclusion for modelled data on vehicle fires in section 7.17.1.2.8.

It is not clear to the eMSCA, whether the assumption of sufficient ventilation systems in tunnels is valid for old tunnels and garages which were built before the actual safety rules came into force. This question however goes beyond the scope of the substance evaluation under REACH.

With the exception of the KBA experiments which stopped monitoring immediately upon detection of the ignition, no monitoring results for HF exposures in cases of vehicle fires and no detailed modelling for these situations have been found. The upper concentration limits given by the theoretical mass of HF which could be produced in fire events are very high.

In the case of a vehicle fire, also bystanders, non-professional first responders and 'good Samaritans' may be exposed to degradation products of polyhaloalkene. An analysis of these situations is not included into the scenarios discussed in (Gradient, 2009b; Gradient, 2013). In the case of good Samaritans, HF exposure above 95 ppm has to be assumed due to the high releases in case of a vehicle fire. HF exposure of bystanders above 95 ppm has to be assumed, too, if it cannot be excluded, e.g. by dispersion modelling. In addition, exposure to COF_2 has to be considered in all cases of thermal degradation of polyhaloalkene.

Conclusion

The estimation that the scenarios above may produce HF exposures above 95 ppm is supported. Exposure of good Samaritans and non-professional first responders should be included into the scenarios. If bystander exposure cannot be excluded (e.g. based on dispersion modelling) it should be included into the scenarios, too.

7.17.2. Environment

Only a short executive summary for each life cycle step is provided is reported in this place due to potential CBI.

Exposure Scenario 1: Industrial use, heat transfer fluids – refrigerants, coolants

The results of the environmental exposure assessment seem to describe a very conservative worst-case situation at local scale regarding the amount of substance used annually. The amount used for calculation is much higher than the value named in the Exposure Scenario. This results in a PEC that will be much higher than in a real site. Even in this worst-case the risk characterisation ratio (RCR) calculated from PEC and PNEC is well below 1 for the effected environmental compartments.

The emission factors used for calculation are not the ones of ERC 7. The registrants provided the information that the emissions resulting from coupling/decoupling-processes during filling of the coolant circuit are compliant with the specifications of several European and international norms without quantifying the releases appropriately. Therefore this information can not be associated with the release factors used for calculation. The release factors used by the registrants for exposure estimation seem to originate from the TGD on Risk Assessment, Part II (Joint Research Center, 2003). As this guidance document was used for exposure estimation during the previous registration program (Directive 67/548/EC) the use of these emission factors is acceptable.

The review of the Exposure Scenario provided by the registrant together with the calculations carried out for validation lead to the conclusion that emissions from filling operations at industrial sites will not cause negative effects in the affected environmental compartments.

Exposure Scenario 2: professional use, heat transfer fluids – refrigerants, coolants

This exposure scenario describes the activities and processes covered when professional workers servicing mobile or stationary air conditioning or refrigeration equipment. The argument of the registrant - even when the charging quantities differ in frequencies and professional settings the used equipment is similar to the ones used during industrial refrigerant charging or packaging – is conclusive under aspects of environmental exposure estimation.

Like in exposure scenario 1 the registrants used very conservative assumptions regarding the annually used amounts at local scale and the number of emission days per year. While the emissions to air are calculated for a scenario of wide dispersive use the number of emission days for the aquatic compartment is lower. This will lead to higher local concentrations for the aquatic compartment during the emission period.

The exposure scenario does not provide any information for releases to air or water but contains PECs for these compartments which match the regional background concentration. The registrant did not provide any justification for this discrepancy.

Therefore final validation of the PECs is not possible. A calculation for validation with the conditions of use from the exposure scenario reveals a PECfreshwater being three orders of magnitude higher than the PEC(freshwater) submitted by the registrants. The calculated value for PECair is nearly the same like the one from the exposure scenario.

In their final conclusion registrant's calculated PECs differ from the results of the assessment carried out during substance validation. Nevertheless there will not be a risk because the RCR will remain well below 1.

Exposure Scenario 3: Formulation of preparations

The exposure scenario describes the activities and processes covered when workers blend various types of refrigeration substances and load products into isocontainers or tanks. The emission factors assumed by the registrant differ from the ones used in the other exposure scenarios. Here the registrant should provide further information because he states that the equipment used for formulation and filling is similar.

7.18. Risk characterisation

7.18.1. Human health

7.18.1.1. **Workers**

No concern with regards to occupational exposure to polyhaloalkene was identified during the evaluation. Therefore, this part of risk characterisation was not part of the substance evaluation.

7.18.1.2. **Consumers**

Introductory note

In this section, as in the corresponding parts throughout this report, no judgement is given on the likelihood of a specific accidental scenario or of the occurrence of physico-chemical events needed for e.g. thermal decomposition of polyhaloalkene into HF and/or COF_2. Consequently, risk characterisation will be limited to the assessment of risks for the case that a given scenario occurs, but no statement will be made with respect to the likelihood of occurrence of this scenario.

Nevertheless, certain assumptions used as premises in the Fault Tree Analysis (FTA) of the Gradient Phase III study (Gradient, 2009b) are not supported by the conclusions of this substance evaluation. These conclusions are related to open questions regarding the role of COF_2 in case of thermal degradation of polyhaloalkene and regarding bystander exposure. The information requirements proposed by the eMSCA would have helped to clarify these issues. Without this information, Fault Tree Analyses (FTA) and Failure Mode and Effect analyses for uses of polyhaloalkene should consider bystander exposure and use conservative limit values for HF that account for possible co-exposure to COF_2 in the scenarios that include thermal degradation of polyhaloalkene or open fire. A revision of the respective parts of the FTA by Gradient (2009b and 2013) could also affect the resulting probability estimates for health effects.

7.18.1.2.1. Scenario 1: Exposure to polyhaloalkene after refrigerant release into a vehicle's passenger cabin

The basic assumptions for this scenario were as follows: Polyhaloalkene can enter the passenger cabin as a consequence of leaks from the mobile air conditioning (MAC) system. Leaks can be small or large (or very large). Small leaks can be induced over time by corrosion and are not necessarily detected during servicing of the MAC. Large-size leaks might in theory arise from small leaks by further corrosion, but those leaks would be detected during servicing of the MAC. Also the bulk of refrigerant would already have been released from the MAC when the leak was still small. Therefore, large leaks are more likely

to occur as the consequence of accidental technical failure of the MAC system or as the result of a vehicle collision.

Relevant leak sizes and corresponding release rates are given in Table 37 above (section 7.17.1.2.4). Leak sizes assumed as typical and evaluated in various monitoring and modelling studies were 0.01 mm (small), 0.1 mm (medium), 0.5 mm (large), and 6.5 mm (very large). In Table 47, the results of the exposure assessment are compared with the relevant DNELs (cf. section 0) in order to calculate the resulting Risk Characterisation Ratios (RCRs). The confidential annex contains a confidential version of the table including information from the CSR.

Table 47

MODELLED AND MONITORED POLYHALOALKENE CONCENTRATIONS IN THE CABIN AFTER AC LEAKS OF DIFFERENT SIZES					
Conditions	**Exposure time**	**Avg. conc. of polyhaloalkene (ppm)**	**Source**	**DNEL (ppm)**	**RCR***
Small leaks (0.01 mm)					
Modelled concentration in lower part of passenger compartment, blower speed low, 1.7 ACH, 2.5 m³	5 min	16	(Gradient, 2009b)	9 200	0.0017
ConsExpo constant rate modelling for 400 g charge, 1.25 m³ 6 ACH, leak rate 0.00036 g/s	15 min	36	This report	6 400	0.006
ConsExpo constant rate modelling for 400 g charge, 1.25 m³, 2 ACH, leak rate 0.00036 g/s	15 min	110	This report	6 400	0.017
Modelled concentration in lower part of passenger compartment, blower speed low, 1.7 ACH, 2.5 m³	30 min	16	(Gradient, 2009b)	5 000	0.003
ConsExpo constant rate modelling for 400 g charge, 1.25 m³,6 ACH, leakage rate 0.00036 g/s	2 h	34	This report	2 900	0.012
ConsExpo constant rate modelling for 400 g charge, 1.25 m³,2 ACH, leakage rate 0.00036 g/s	2 h	84	This report	2 900	0.029
Medium-sized leaks (0.1 mm)					
Modelled concentration in lower part of passenger compartment, blower speed low, 1.7 ACH, 2.5 m³	5 min	3 800	(Gradient, 2009b)	9 200	0.4
ConsExpo constant rate modelling for 400 g charge, 1.25 m³, 6 ACH, leak rate 0.03 g/s	15 min	3 000	This report	6 400	0.5
ConsExpo constant rate modelling for 400 g charge, 1.25 m³, 2 ACH, leak rate 0.03 g/s	15 min	9 000	This report	6 400	1.4
Modelled concentration in lower part of passenger compartment, blower speed low, 1.7 ACH, 2.5 m³	30 min	3 700	(Gradient, 2009b)	5 000	0.7
ConsExpo constant rate modelling for 400 g charge, 1.25 m³, 6 ACH, leakage rate 0.03 g/s	2 h	2 800	This report	2 900	1.0
ConsExpo constant rate modelling for 400 g charge, 1.25 m³, 2 ACH, leakage rate 0.03 g/s	2 h	7 100	This report	2 900	2

MODELLED AND MONITORED POLYHALOALKENE CONCENTRATIONS IN THE CABIN AFTER AC LEAKS OF DIFFERENT SIZES					
Conditions	**Exposure time**	**Avg. conc. of polyhaloalkene (ppm)**	**Source**	**DNEL (ppm)**	**RCR***
Large and very large leaks					
Analyses from 24 samples near drivers´ face after refrigerant release into passenger cabin, different vehicles and air modes, leak rates 1.14, 12.4, or 13 g/s, sampling time not given	5 min	0-50 300	(Gradient, 2009b)	9 200	0-5
Modelled concentration in lower part of passenger compartment, 0.5 mm leak, blower speed low, 1.7 ACH, 2.5 m³	5 min	63 500	(Gradient, 2009b)	9 200	7
Modelled concentration in lower part of passenger compartment, 6.35 mm, blower speed low, 1.7 ACH, 2.5 m³	5 min	70 600	(Gradient, 2009b)	9 200	8
ConsExpo constant rate modelling for collision scenarios	Cf. additional information in confidential annex				
Modelled concentration in lower part of passenger compartment 0.5 mm leak, blower speed low, 1.7 ACH, 2.5 m³	30 min	58 400	(Gradient, 2009b)	5 000	12
Modelled concentration in lower part of passenger compartment, 6.35 mm leak, blower speed low, 1.7 ACH, 2.5 m³	30 min	64 800	(Gradient, 2009b)	5 000	13

* rounded value

Evaluation

Strengths and limitations of the different modelling and monitoring approaches have been discussed in the section on consumer exposure. The following conclusions can be drawn from the above results (see confidential annex for a text version which includes the information from the CSR):

- All calculations for small leaks resulted in RCRs clearly < 1.
- In three calculations for medium-size leaks, RCRs of 1, 1.4, or 2 were calculated. The RCR of 1.4 relates to a scenario with 15 min exposure. However, the corresponding modelled exposure concentration was still 11-fold lower than the relevant NOAEC of ≥ 100 000 ppm from the acute toxicity study in rabbits, while the acute LOAEC for that species is not known and may or may not be considerably higher (in rats – albeit shown to be less sensitive to polyhaloalkene toxicity than rabbits - no effects within the first two hours of exposure were noted up to 400 000 ppm, the highest dose tested). Moreover, extrapolation to 15 min exposure is associated with considerable additional uncertainty.
- The RCRs of 1 and 2 relate to scenarios with 2 h exposure and are 7- and 18-fold lower than the LOAEC of 50 000 ppm (observed in the RDT studies in rats) and 28- and 71-fold lower than the relevant LOAEC of 200 000 ppm in rats (laboured breathing in the acute study in rats, first observed two hours into the study).
- For large or very large leaks, both modelled and measured data as reported in (Gradient, 2009b) frequently resulted in RCRs greater than 1 (range 0–13). Only acute scenarios (i.e. with the same DNEL basis as for medium-size leaks) had to be considered. It is noted that the measured data were determined after a potentially

unrealistic full refrigerant discharge into the passenger cabin and the uniform mixing model calculations overestimated the exposure in the driver´s breathing zone. A more recent exposure modelling by the registrant resulted in lower RCRs based on the assumption that only a much lower fraction of the total refrigerant charge would be available for release (cf. confidential annex to this report).

In summary, it must be understood that in real life a complex set of parameters will determine actual polyhaloalkene concentrations in the passenger cabin, which depend strongly on the vehicle design as well as the nature of the accident (as different types of car crashes will go alanog with significantly different damage to the vehicle).

Conclusion

Given the uncertainties inherent in exposure modelling as well as in DNEL derivation, the eMSCA finds that the above results do not give rise to a strong concern regarding a relevant risk for the general public posed by medium-size leaks. For large/very large leaks a higher theoretical risk is shown. This information supports the international standards SAE J 2773 and ISO 13043 that inter alia require an evaluation for polyhaloalkene releases to the passenger compartment of cars in the case of large leaks of the air conditioning (AC) system. Also, this information should be taken into account in a FTA-/FMEA-based risk analyses.

7.18.1.2.2. Scenario 2: Exposure to thermal degradation products of polyhaloalkene after a refrigerant release into the passenger cabin and subsequent ignition

Evaluation

No modelling data are available for this scenario. It has been addressed in the experimental designs by (Hughes, 2009b) for ignition by a butane lighter which gave a maximum HF concentration of 34.5 ppm, which is below the relevant DNELs of 68/34 ppm for 2/10 min exposure.

However, the maximum concentration of polyhaloalkene in these experiments was 4.2%, while higher concentrations had been monitored by OEMs. Therefore, somehow higher HF concentrations are conceivable in cases of refrigerant release into the passenger cabin and it has been included into the fault tree analysis by (Gradient, 2009b) for the case of a collision. In contrast, the non-collision-induced AC leak was not included because polyhaloalkene was assumed to evaporate slowly without reaching the lower flammability limit. Also the smoking scenario (a person smokes in the passenger cabin after an AC leak to the cabin has occurred) has not been included in the fault tree analysis. The experimental results gave HF concentrations around 10 ppm, but raised a number of questions with regard to the validity of the experimental design and the quality of reporting.

Conclusion

In conclusion, the eMSCA notes that the results obtained for this scenario do not indicate an unacceptable risk with respect to HF. However, as demonstrated in section 7.17.1.2.6 above, the measured HF concentrations are likely to include an unknown, possibly significant amount of COF_2 and therefore using the DNELs for HF as the toxicological benchmark may significantly underestimate risk. Use of a more realistic, lower exposure limit for HF which accounts for COF_2 toxicity is therefore recommended for FTAs/FMEAs.

7.18.1.2.3. Scenario 3: Exposure to thermal degradation products of polyhaloalkene after an AC leak to the engine compartment or collision and contact of polyhaloalkene with hot surfaces

Evaluation

The results of the evaluation by (Gradient, 2009b) are given in Table 44 above (section 7.17.1.2.9). It has been addressed in the monitoring studies by (Hughes, 2009a) and (KBA, 2013). The data demonstrate critical HF concentrations, in particular for scenarios including

ignitions. The estimation by (Gradient, 2009b) that the above-mentioned scenarios may produce HF exposures above 95 ppm is supported. However, the argumentation that HF concentrations outside the engine bay will not exceed 95 ppm in the case of contact of polyhaloalkene to hot surfaces is not supported by the data of (KBA, 2013). In particular, exposure of bystanders to HF above 95 ppm cannot be excluded in case of an ignition.

The authors of the (Gradient, 2009b) study chose a possible exposure to HF levels exceeding 95 ppm, the 10 min AEGL-2, as a criterion for including scenarios into the Fault Tree Analysis (FTA). The AEGL-2 is equivalent to about the 1.5-fold of the 2 minute DNEL for severe effects established in this report (and to the 2.5-fold of the 10 minute DNEL). Exceedance of the AEGL-2 therefore corresponds to RCRs > 1.5 for a 2 min exposure and RCRs > 2.5 for a 10 min exposure.

Conclusion

In conclusion the eMSCA notes that the results obtained for this scenario already indicate several situations of unacceptable risk with respect to HF that were included into the FTA by (Gradient, 2009b). However, exposure of bystanders should be additionally considered in all scenarios with thermal degradation of polyhaloalkene.

In addition, as demonstrated in section 7.17.1.2.6 above, the measured HF concentrations are likely to include an unknown, possibly significant amount of COF_2 and therefore using the DNELs for HF as the toxicological benchmark may significantly underestimate risk. Use of a more realistic, lower exposure limit for HF which accounts for COF_2 toxicity is therefore recommended for FTAs/FMEAs and a revision of the health limits in ISO 13043 should be considered.

7.18.1.2.4. Scenario 4: Exposure to thermal degradation products of polyhaloalkene in cases of vehicle fire

Evaluation

As explained above in Table 45 in section 7.17.1.2.9, the conclusion of the FTAs performed in (Gradient, 2009b) that vehicle occupants or others may be exposed to HF at levels above 95 ppm is supported. However, the upper concentration limits given by the theoretical mass of HF which could be produced in fire events are very high. In the case of a vehicle fire, also bystanders, non-professional first responders and 'good Samaritans' may be exposed to degradation products of polyhaloalkene, but an analysis of these situations is not included into the scenarios discussed in (Gradient, 2009b; Gradient, 2013).

Conclusion

In conclusion, the eMSCA notes that the results obtained for this scenario already indicate several situations of unacceptable risk with respect to HF that were included into the FTA by (Gradient, 2009b). In addition, as demonstrated in section 7.17.1.2.6 above, the measured HF concentrations are likely to include an unknown, possibly significant amount of COF_2 and therefore using the DNELs for HF as the toxicological benchmark may significantly underestimate risk. Use of a more realistic, lower exposure limit for HF which accounts for COF_2 toxicity is therefore recommended for FTAs/FMEAs and a revision of the health limits in ISO 13043 should be considered.

In addition, the situation of bystanders and 'good Samaritans' has not been considered in (Gradient, 2009b) to the extent deemed necessary by the eMSCA. A revision of the scenarios including realistic estimates of the temporal and spatial distribution of HF (and COF_2) and of the exposure levels relevant for exposure of individuals present at various distances from the engine compartment (e.g. good Samaritans will position themselves at the side of the car while trying to rescue injured accident victims, bystanders might watch the scene from a certain distance etc.) is recommended in order to adequately assess the risk for the general population. Such calculations should be performed for open air locations as well as for confined spaces such as tunnels or garages.

7.18.2. Environment

The derivation of the PEC/PNEC ratio for the different identified uses was not part of the initial evaluation as no concern has been identified in this regard. As a result of the assessment of the intrinsic substance properties, there is no evidence that under the conditions of intended uses the concentrations of Polyhaloalkene in the environment will aggregate to equilibrium concentrations that rise above the PNECs. The high vapour pressure and the high volatility from water lead to the circumstance that the majority of polyhaloalkene will end up in the atmosphere when released to any environmental compartment where it will be suspect to abiotic photochemical degradation processes.

Due to the relatively short degradation hal-life in the atmosphere of about 2 days up to 14 days, the investigations of risks resulting from release of polyhaloalkene into the environment should focus on the degradation products. From the data available, trifluoroacetic acid (TFA) was identified as major transformation product for the environment.

Additional remark for TFA

When the PECs for TFA (published by Henne etal., 2008) is taken as a basis, the environmental concentrations of TFA resulting from degradation of polyhaloalkene still are well below the PNECs of TFA reviewed and considered applicable by the eMSCA. Therefore, no risk characterisation ratio above 1 will be the result. **However, based on the persistency and mobility of TFA, the eMSCA considers further minimisation of emissions to the environment of sources of TFA necessary.**

7.19. Abbreviations

2-AAF	2-Acetylaminofluorene
AC	Air-conditioning/conditioner
ACH	Air changes per hour
ADME	Absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIT	Autoignition temperature
ANCOVA	Analysis of covariance
ASHRAE	American Society of Heating, Refrigerating and Air-Conditioning Engineers
ATEL	Acute Toxicity Exposure Limit
AUC	Area-under-the-curve
BAuA	German Federal Institute for Occupational Safety and Health
BfC	German Federal Office for Chemicals
BoA	Board of Appeal
CA	Competent authority
CAS	Chemical Abstracts Service
C&L	Classification & labelling
CLH	Harmonised Classification & Labelling
CLP	Regulation (EC) 1272/2008 on the Classification, labelling, and packaging of substances and mixtures
CoRAP	Community rolling action plan
CSR	Chemical Safety Report
CYP	Cytochrome P
DNA	Deoxyribonucleic acid
DNEL	Derived no effect level
ECHA	European Chemicals Agency
EDSTAC	Endocrine Disruptor Testing and Screening Advisory Committee
eMSCA	Evaluating Member State Competent Authority
ECG	Electrocardiogram
ED	Endocrine disruption/disruptor
EDSP	Endocrine disruptor screening program
EU	European Union
F	Female
FMEA	Failure Mode and Effect Analysis

FTA	Fault tree analysis
FT-IR	Fourier-Transform Infrared (spectroscopy/spectrometer)
GD	Gestation day
GLP	Good Laboratory Practice
GSH	Glutathione
HFC	Hydrofluorocarbon
i.p.	Intraperitoneal
ISO	International Organization for Standardization
IUCLID	International Uniform Chemical Information Database
JRC	(Directorate-General) Joint Research Centre (of the European Commission)
KBA	Kraftfahrtbundesamt (German Motor Transport Authority)
LC	Lethal Concentration
LC/MS-MS	Liquid Chromatography with tandem mass spectrometry
LOAEC	Lowest-Observed-Adverse-Effect-Concentration
LOAEC	Lowest-Observed-Adverse-Effect-Concentration
M	Male
MAC(S)	Mobile air-conditioning (system)
MDPV	Medium-Duty Passenger Vehicle
MMC	Mitomycin C
MMS	Methyl methane sulfonate
MN	Micronucleus
MS	Member State
MSC	Member State Committee
MSCA	Member State Competent Authority
N/A	Not applicable
NADPH	Nicotinamide adenine dinucleotide phosphate
NOAEC	No-Observed-Adverse-Effect-Concentration
NOEC	No-Observed-Effect-Concentration
NTP	National Toxicology Program
NZW	New Zealand White
OECD	Organization for Economic Co-Operation and Development
OEM	Original equipment manufacturers
PBTK	Physiology-based Toxicokinetics
PC	Partition coefficient
PFAS	Per- and polyfluoroalkyl substance(s)
PND	Post-natal day
PNDT	Prenatal Developmental Toxicity
PoD	Point of departure
RCR	Risk characterisation ratio
REACH	Regulation (EC) 1907/2006 on the registration, evaluation, authorisation, and restriction of chemicals
SD	Stabdard deviation
SAE	Society of Automotive Engineers
SEv	Substance evaluation
SPF	Specified pathogen-free
STOT	Specific Target Organ Toxicity
SVHC	Substance of very high concern
TFA	Trifluoroacetic acid
TFEA	Tetrafluoroethane
TFEL	Tetrafluoroethylene
TGR	Transgenic rodent somatic and germ cell mutagenicity assay
TWA	Time-weighted average
UDS	Unscheduled DNA synthesis
USEPA	United States Environmental Protection Agency
VO	Vaginal opening

7.20. References

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