Committee for Risk Assessment

RAC

Annex 1
Background document
to the Opinion proposing harmonised classification and labelling at EU level of

tris(2-methoxyethoxy)vinylsilane; 6-(2-methoxyethoxy)-6-vinyl-2,5,7,10-tetraoxa-6-silaundecane

EC Number: 213-934-0

CAS Number: 1067-53-4

CLH-O-0000001412-86-207/F

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

8 June 2018

CLH report

Proposal for Harmonised Classification and Labelling

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

International Chemical Identification:

Tris(2-methoxyethoxy)vinylsilane

EC Number: **213-934-0**

CAS Number: **1067-53-4**

Index Number: **-**

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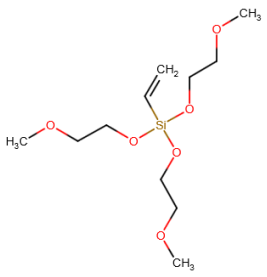
Version number: 02 **Date: May, 3rd 2017**

CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

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

Name(s) in the IUPAC nomenclature or other international chemical name(s)	6-(2-Methoxyethoxy)-6-vinyl-2,5,7,10-tetraoxa-6-silaundecane
Other names (usual name, trade name, abbreviation)	Tris(2-methoxyethoxy) vinylsilane 2,5,7,10-Tetraoxa-6-silaundecane, 6-ethenyl-6-(2-methoxyethoxy)-; 6-(2-Methoxyethoxy)-6-vinyl-2,5,7,10-tetraoxa-6-silaundecane; 6-(2-Methoxyethoxy)-7-silyl-2,5,8,11-tetraoxadodec-6-ene; Ethenyl-tris(2-methoxyethoxy)silane; Methoxyethoxyvinylsilane; Vinyl tris(2-methoxyethoxy)silane VTMOEOS
ISO common name (if available and appropriate)	*Not applicable*
EC number (if available and appropriate)	213-934-0
EC name (if available and appropriate)	Tris(2-methoxyethoxy)vinylsilane
CAS number (if available)	1067-53-4
Other identity code (if available)	*Not available*
Molecular formula	$C_{11}H_{24}O_6Si$
Structural formula	
SMILES notation (if available)	COCCO[Si](OCCOC)(OCCOC)C=C
Molecular weight or molecular weight range	280.391 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	*Not applicable*
Description of the manufacturing process and identity of the source (for UVCB substances only)	*Not applicable*

Degree of purity (%) (if relevant for the entry in Annex VI)	*2-Methoxyethanol was identified as a potential impurity (1 %) (OECD, 2006)*

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)
Tris(2-methoxyethoxy)vinylsilane	Mono-constituent	No harmonised classification	Repr. 1B, H360Df; dissem. Registration database file, last modified 19 October 2016 (ECHA, 2017b)

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
According to OECD (2006), section 1.2 and according to the SIDS-dossier (data compilation file), sections 1.1.1 and 1.3, attached to OECD (2006): puritiy 99 %; impurities: 1 % (1 % (2-methoxyethanol, CAS 109-86-4), cited from: Silicones Environmental Healh and Safety Council, 2005 (unpublished). 2-methoxyethanol is classified (CLH, Annex VI, Table. 3.1): Flamm. Liq. 3, Acute Tox. 4*, Repr. 1B; H226, H302, H312, H332, H360FD (ECHA, 2017a).				

"No impurities relevant for classification " according to dissem. Registration database file, last modified 19 October 2016 (ECHA, 2017b)

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
No data available					

"No additives relevant for classification" according to dissem. Registration Database File, last modified 19 October 2016 (ECHA, 2017b)

Table 5: Test substances (non-confidential information) (this table is optional)

Identification of test substance	Purity	Impurities and additives (identity, %, classification if available)	Other information	The study(ies) in which the test substance is used
No data available				

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 6: Proposed harmonised classification and labelling according to the CLP criteria

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	--	Tris(2-methoxyethoxy) vinylsilane	213-934-0	1067-53-4	No entry						
Dossier submitters proposal			213-934-0	1067-53-4	Repr. 1B	H360FD	Danger GHS08	H360FD	-	-	-
Resulting Annex VI entry if agreed by RAC and COM											

Table 7: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	*hazard class not assessed in this dossier*	No
Flammable gases (including chemically unstable gases)	*hazard class not assessed in this dossier*	No
Oxidising gases	*hazard class not assessed in this dossier*	No
Gases under pressure	*hazard class not assessed in this dossier*	No
Flammable liquids	*hazard class not assessed in this dossier*	No
Flammable solids	*hazard class not assessed in this dossier*	No
Self-reactive substances	*hazard class not assessed in this dossier*	No
Pyrophoric liquids	*hazard class not assessed in this dossier*	No
Pyrophoric solids	*hazard class not assessed in this dossier*	No
Self-heating substances	*hazard class not assessed in this dossier*	No
Substances which in contact with water emit flammable gases	*hazard class not assessed in this dossier*	No
Oxidising liquids	*hazard class not assessed in this dossier*	No
Oxidising solids	*hazard class not assessed in this dossier*	No
Organic peroxides	*hazard class not assessed in this dossier*	No
Corrosive to metals	*hazard class not assessed in this dossier*	No
Acute toxicity via oral route	*hazard class not assessed in this dossier*	No
Acute toxicity via dermal route	*hazard class not assessed in this dossier*	No
Acute toxicity via inhalation route	*hazard class not assessed in this dossier*	No
Skin corrosion/irritation	*hazard class not assessed in this dossier*	No
Serious eye damage/eye irritation	*hazard class not assessed in this dossier*	No
Respiratory sensitisation	*hazard class not assessed in this dossier*	No
Skin sensitisation	*hazard class not assessed in this dossier*	No
Germ cell mutagenicity	*data conclusive but not sufficient for classification*	Yes
Carcinogenicity	*data lacking*	No
Reproductive toxicity	*harmonised classification proposed*	Yes
Specific target organ toxicity-single exposure	*hazard class not assessed in this dossier*	No
Specific target organ toxicity-repeated exposure	*hazard class not assessed in this dossier*	No
Aspiration hazard	*hazard class not assessed in this dossier*	No
Hazardous to the aquatic environment	*hazard class not assessed in this dossier*	No
Hazardous to the ozone layer	*hazard class not assessed in this dossier*	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

Tris(2-methoxyethoxy)vinylsilane has not been classified by the Dangerous Substances Directive (Dir. 67/548/EEC) and has no entry in Annex VI Tables 3.1 and 3.2 of the Regulation (EC) No. 1272/2008 (CLP Regulation) (ECHA, 2017a).

As stated by ECHA (10 September 2012; Decision number: TPE-D-0000002236-79-05/F) the Registrant had self-classified the registered substance as a Repr 2; H361f (CLP) (Repr. Cat.3 (R62); DSD) and submitted a testing proposal (pre-natal developmental toxicity study (OECD Guideline 414)) in accordance with Articles 10(a)(ix) and 12(1)(e) of the REACH Regulation. ECHA decided that the Registrant shall carry out this pre-natal developmental toxicity study in rats, oral route (Annex IX, 8.7.2.,test method: EU B.31/OECD 414) and submit an update of the registration dossier containing the information required by this decision to ECHA by 10 September 2013. However, ECHA also pointed out, that Column 2 of Annex IX of the REACH Regulation allows a registrant to adapt the standard information requirement for developmental toxicity study if a substance is known to cause developmental toxicity, meeting the criteria for toxic to reproduction category 1A or 1B: May damage the unborn child (H360D) and the available data are adequate to support a robust risk assessment. If the conditions for the above adaption are met and full justification is provided by the Registrant in the dossier, in accordance with column 2 of Annex IX, the developmental toxicity study would not be needed.

Finally, the Registrant has not performed the OECD 414 study suggested by ECHA, but revised his CSR and disseminated database file by August 2014 with a self-classification of Tris(2-methoxyethoxy)vinylsilane as a Repr. 1B (H360Df) substance. This has been acknowledged and reported by ECHA (Analysis of the most appropriate risk management option (RMOA); 06. 06. 2016).

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

There is no requirement for justification that action is needed at Community level.

RAC general comment
Although there are no *in vivo* studies available on the metabolism of tris(2-methoxyethoxy)vinylsilane in mammals, a well-conducted *in vitro* hydrolysis study (GLP compliant, OECD TG 111) demonstrated fast and effective hydrolysis of the parent compound to 2-methoxyethanol and vinylsilanetriol at physiological pH values. It may be assumed that this hydrolysis also takes place *in vivo* in mammals, especially under acidic conditions of the stomach (ECHA, 2012; 2016; OECD, 2006). This hydrolysis step is relevant for the hazardous properties of tris(2-methoxyethoxy)vinylsilane because of the inherent toxicological properties of 2-methoxyethanol, a substance already harmonised in the CLP Regulation as Repr. 1B for fertility and developmental toxicity. However, from the results of structure activity relationship analysis presented by the dossier submitter (DS) in the background document, it may not be excluded that tris(2-methoxyethoxy)vinylsilane is also metabolised via other pathways. Therefore, quantitative conclusions on the relevance of 2-methoxyethanol as a critical metabolite for the classification of tris(2-methoxyethoxy)vinylsilane are not possible.

5 IDENTIFIED USES

Tris(2-methoxyethoxy)vinylsilane is used for a variety of different applications. It serves as a crosslinking, binding and coupling agent and as a surface modifier. It is also used as a monomer in the production of silicone polymers. Tris(2-methoxyethoxy)vinylsilane is used for the production of rubber and plastics, for the formulation and use of non-metal surface treatment solutions/dispersions, and for the formulation of sealants (RMOA; ECHA, 2016).

6 DATA SOURCES

Critical data reported in this CLH report were taken from secondary sources, if not stated otherwise.

These secondary sources were

a) the disseminated database file on tris(2-methoxyethoxy)vinylsilane, last modified 19 October 2016 (ECHA, 2017b), and/ or

b) the OECD SIDS Initial Assessment Report including SIDS dossier (OECD, 2006).

The confidential registration dossier was consulted for information on potential discrepancies and supplements (Annex I), but no confidential information was transferred to the CLH report.

ECHA's decision on further testing of tris(2-methoxyethoxy)vinylsilane (ECHA, 2017b) and subsequent ECHA analysis of the most appropriate risk management option (RMOA; ECHA, 2016) were used to present follow up information.

In addition, scientific reviews and selected original study reports have been consulted to characterise critical toxicological properties of a major hydrolysis product (assumed metabolite) of tris(2-methoxyethoxy) vinylsilane, i.e., 2-methoxyethanol (Chapin et al., 1985; Nelson et al., 1989; WHO, 1990; 2009).

Furthermore, ECHA guidance documents on the application of CLP criteria and on the preparation of dossiers for harmonised classification and labelling were used to compile this report (ECHA, 2014; 2015).

Searches for publications and other relevant data were performed based on the following databases:

- U.S. National Library of Medicine, Pubmed.gov[1]
- U.S. National Library of Medicine, TOXNET, ChemID*plus*[2]
- Chemical Abstracts (at host STN International Europe[3])
- SciSearch, Biosis, CAB Abstracts, Embase (at host Deutsches Institut für Medizinische Dokumentation und Information, DIMDI[4])
- Experimental data on specific substances as documented in OECD Application Toolbox (OECD, 2016),

in addition to unspecific databases (e.g., *google scholar*).

All references used in this report are also listed in section 14.

7 PHYSICOCHEMICAL PROPERTIES

Table 8: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and	liquid	Design Institute for	At standard temperature and

[1] https://www.ncbi.nlm.nih.gov/pubmed
[2] https://chem.nlm.nih.gov/chemidplus/
[3] http://www.stn-international.de/index.php?id=123 ; https://www.fiz-karlsruhe.de/
[4] https://www.dimdi.de/static/de/db/

Property	Value	Reference	Comment (e.g. measured or estimated)
101,3 kPa		Physical Property Data, 2005 from (ECHA, 2017b)	pressure
Melting/freezing point	-130 °C	Company data, 2010 from (ECHA, 2017b)	Measured at 1013 hPa
Boiling point	285 °C	Design Institute for Physical Property Data, 2005 from (ECHA, 2017b)	Measured at 1013 hPa
Relative density	1.03 g/cm³	Company data, 2007 from (ECHA, 2017b)	Measured at 25 °C
Vapour pressure	0.434 Pa	Company data, 2010 from (ECHA, 2017b)	Measured at 25 °C
Surface tension	No data	(ECHA, 2017b)	On the basis of structure the substance is not expected to be surface active
Water solubility	71479 mg/L (very soluble)	QSAR method and prediction reporting tools, 2009 from (ECHA, 2017b)	QSAR analysis at 20 °C and pH 7
Partition coefficient n-octanol/water	0.26	QSAR method and prediction reporting tools, 2009 from (ECHA, 2017b)	QSAR analysis at 20 °C and pH 7
Flash point	115 °C	Company data, 2008 from (ECHA, 2017b)	Measured at 1013 hPa
Flammability	No data	(ECHA, 2017b)	On the basis of structure and previous experience in handling and use, the substance is not expected to be flammable in conctact with air or water
Explosive properties	No data	(ECHA, 2017b)	The substance has no chemical groups that are associated with explosive properties
Auto-ignition temperature	210 °C	Haas. H, 1995 from (ECHA, 2017b)	
Oxidising properties	No data	(ECHA, 2017b)	On the basis of chemical structure, the substance is expected to be incapable of reacting exothermically with combustible materials
Granulometry	No data	(ECHA, 2017b)	On the basis that the substance is marketed and used in a non solid form, the granulometry study does not need to be conducted.
Stability in organic solvents and identity of relevant degradation products	No data		
Dissociation constant	No data	(ECHA, 2017b)	On the basis that the substance is hydrolytically unstable (half-life less than 12 hours) the dissociation constant study does not need to be conducted.
Viscosity	2.3 mPa s	Company data, 2007 from (ECHA, 2017b)	Measured at 25 °C

8 EVALUATION OF PHYSICAL HAZARDS

Evaluation not performed for this substance

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

No information from human or animal data on toxicokinetics of tris(2-methoxyethoxy)vinylsilane is available. Experimental studies on effects after dermal and oral exposure demonstrate systemic health effects and therefore indicate bioavailability. Data on bioavailability after inhalation exposure are lacking. However, in the disseminated registration database a subchronic inhalation study with exposure of experimental animals to the structurally related vinyltrimethoxysilane is reported, showing systemic effects also from this exposure pathway for this substance (ECHA, 2017b; Thomas, 1976).

An OECD Test Guideline 111 – study on hydrolysis (as a function of pH) has been performed:

Dissipation half-life of the parent compound was 1.6 minutes at pH 4 and 25°C, with a hydrolysis rate constant of 0.43 min^{-1}, 62 minutes at pH 7 and 25°C, with a hydrolysis rate constant of 0.011 min^{-1} and 0.9 minutes at pH 9 and 25°C, with a hydrolysis rate constant of 0.73 min^{-1}. Hydrolysis rates increased as a function of temperature ((pseudo-) first order hydrolysis). 2-Methoxyethanol (CAS no. 109-86-4) and vinylsilanetriol were observed transformation products (ECHA, 2017b).

OECD (2006) comments and analyses for environmental conditions: “the material hydrolyzes and condenses, producing 3 moles of 2-methoxyethanol and 1 mole of vinylsilantriol for each mole of parent silane.”

In a attempt to gain further information, metabolism simulators (*in vivo* rat metabolism, rat liver S9 metabolism, skin metabolism) were applied to the target substance using “structural activity relationship” (SAR) tools (OECD, 2016). These SAR tools did not identify 2-methoxyethanol and vinylsilanetriol from hydrolysis as probable metabolites. Instead, each of the rat metabolism simulators identified 7 possible metabolites, whereas the skin metabolism simulator identified 3 possible metabolites. This SAR analysis is not qualified to question the relevance of 2-methoxyethanol and vinylsilanetriol from hydrolysis as *in vivo* metabolites of tris(2-methoxyethoxy)vinylsilane, as confidence in the results of the metabolism simulators is limited. However, SAR analysis in combination with lacking toxicokinetic data on tris(2-methoxyethoxy)vinylsilane preclude a firm assumption that 2-methoxyethanol and vinylsilanetriol should be the sole critical metabolites to be considered.

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

No experimental data on toxicokinetic parameters are available. However, indirect evidence from health effects observed after oral and dermal exposure demonstrate systemic uptake after exposure to tris(2-methoxyethoxy)vinylsilane. Systemic uptake may also be assumed from inhalation exposure as evidenced from a similar substance. There are no *in vivo* studies available on metabolism. However, a qualified study on hydrolysis (in compliance with GLP and according to OECD TG 111) demonstrates fast and effective hydrolysis of the parent compound to 2-methoxyethanol and vinylsilanetriol at physiological pH values. It may be assumed that this hydrolysis also takes place *in vivo* in mammals, especially under acidic conditions of the stomach (ECHA, 2012; 2016; OECD, 2006). This metabolic step is relevant because of the inherent toxicological properties of 2-methoxyethanol. However, from the results of SAR-analysis it may not be excluded that tris(2-methoxyethoxy)vinylsilane is also metabolised via other pathways. Therefore, quantitative conclusions on the relevance of 2-methoxyethanol as a critical metabolite are not possible.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

10.1 Acute toxicity - oral route

Evaluation not performed for this substance

10.2 Acute toxicity - dermal route

Evaluation not performed for this substance

10.3 Acute toxicity - inhalation route

Evaluation not performed for this substance

10.4 Skin corrosion/irritation

Evaluation not performed for this substance

10.5 Serious eye damage/eye irritation

Evaluation not performed for this substance

10.6 Respiratory sensitisation

Evaluation not performed for this substance

10.7 Skin sensitisation

Evaluation not performed for this substance

10.8 Germ cell mutagenicity

Table 9: Summary table of mutagenicity/genotoxicity tests *in vitro*

Method, guideline, deviations if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
EU Method B.13/14 Dir. 84/449/EEC, 1984[1)] Bacterial reverse mutation assay Restrictions were that the range of strains does not comply with current guidelines (ECHA, 2017b)	tris(2-methoxyethoxy)-vinylsilane, no information on purity available	S. typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538 ± rat liver S9 (phenobarbital induced); 8, 40, 200, 1000, 5000 µg/plate Vehicle: not specified Positive control: yes	No toxicity observed at any test concentration (cytotoxicity > 5000 µg/plate); precipitation at 5000 µg/plate negative for mutagenicity to bacteria with and without activation under the conditions of this test	NN, 1993 from (ECHA, 2017b) Study: 005, study report
OECD TG 471 Bacterial reverse mutation assay (GLP)	tris(2-methoxyethoxy)-vinylsilane, no information on purity available	S. typhimurium, TA 98, TA 100, TA 1535, TA 1537, ± rat liver S9 (Aroclor induced); 100, 333, 1000, 3333,	No appreciable toxixicity observed; no precipitation observed negative for mutagenicity to bacteria with and without activation under the conditions of this test	NN, 1999 from (ECHA, 2017b) Study: 001,

Method, guideline, deviations if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
		5000 µg/plate Vehicle: DMSO/ solvent control Positive control: yes --- E. coli WP2 uvr A ± rat liver S9 (Aroclor induced) 100, 333, 1000, 3333, 5000 µg/plate Vehicle: DMSO/ solvent control Positive control: yes		study report
(similar to) OECD TG 471 Bacterial reverse mutation assay Study did not meet current guideline requirements, as only three strains of bacteria were tested (ECHA, 2017b)	tris(2-methoxyethoxy)-vinylsilane, no information on purity available	S. typhimurium, TA 97, TA 98, TA 100, ± rat liver S9 (Aroclor induced); 8, 40, 200, 1000, 5000 µg/plate Vehicle: EGDME Positive control: yes	No cytotoxicity, but tested up to limit concentrations negative for mutagenicity to bacteria with and without activation under the conditions of this test	NN, 1988 from (ECHA, 2017b) Study: 004, study report
OECD TG 473 mammalian chromosome aberration test (GLP)	tris(2-methoxyethoxy)-vinylsilane, no information on purity available	Chinese hamster ovary (CHO) ± metabolic activation 350 (toxicity test only), 700, 1400, 2801 µg/ml, 4hrs., 20hrs. treatment Vehicle: DMSO/ solvent control Positive control: yes	No substantial cytotoxicity, but tested up to limit concentrations Mean mitotic index; cells with (numerical or structural) aberrations, no statistical differences from negative control after 4 hrs or 20 hrs of treatment Negative with and without activation under the conditions of this test	NN, 2004 from (ECHA, 2017b) Study: 002, study report
- OECD TG 476 - EU method B17 mammalian cell gene mutation test (GLP)	tris(2-methoxyethoxy)-vinylsilane, no information on purity available	Mouse lymphoma L5178Y cells ± metabolic activation (phenobarbital, beta-naphthoflavone induced) 187.5-3000 µg/ml Vehicle: DMSO/ solvent control Positive control: yes	No substantial cytotoxicity, but tested up to limit concentrations Mutant colonies/10^6 cells below threshold, all concentrations after 4 hrs or 24 hrs of treatment Negative with and without activation under the conditions of this test	NN, 2010 from (ECHA, 2017b) Study: 003, study report

Method, guideline, deviations if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
[1)] http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31984L0449&from=de				

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

All tests (*in vitro*) on mutagenicity/ genotoxicity (bacteria reverse mutation assays, mammalian chromosome aberration test, mammalian cell gene mutation test) performed with tris(2-methoxyethoxy)-vinylsilane provided clearly negative results with or without metabolic activation. Only ambiguous effects with respect to germ cell mutagenicity have been observed for 2-methoxyethanol (WHO, 2009). 2-Methoxyethanol is an assumed metabolite of tris(2-methoxyethoxy)vinylsilane by hydrolysis. 2-Methoxyethanol does not induce gene mutations in *in vitro* investigations. However, there is some indication that it induces clastogenic damage and there is consistent evidence that the initial metabolite 2-methoxyacetaldehyde (MALD) is genotoxic in several cell lines. Results of the available *in vivo* studies suggest that 2-methoxyethanol is not genotoxic in somatic cells. Although there has been some suggestions of an induction of genetic effects in male germ cells, the results from these studies are inconclusive (WHO, 2009). Also, the German commission for biological exposure limits summarises: “the majority of in vitro investigations and animal studies do not indicate genotoxic effects or germ cell toxicity for 2-methoxyethanol” (Drexler and Hartwig, 2009). In agreement with this evaluation, the substance does not have a harmonised classification according to CLP Regulation (EC) No. 1272/2008 (Annex VI) for this endpoint.

10.8.2 Comparison with the CLP criteria

The CLP criteria for classification as germ cell mutagen are defined in the ECHA guidance (ECHA, 2015) as follows:

- *A mutation means a permanent change in the amount or structure of the genetic material in a cell. The term ‘mutation’ applies both to heritable genetic changes that may be manifested at the phenotypic level and to the underlying DNA modifications when known (including specific base pair changes and chromosomal translocations).*

All tests (*in vitro*) on mutagenicity/ genotoxicity (bacteria reverse mutation assays, mammalian chromosome aberration test, mammalian cell gene mutation test) performed with tris(2-methoxyethoxy)-vinylsilane provided clearly negative results with or without metabolic activation. No *in vivo* test results are available.

The CLP-regulation specifies criteria for category 2 substances, which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans:

- *The classification in Category 2 is based on:*
  - *Positive evidence obtained from experiments in mammals and/or in some cases from in vitro experiments, obtained from:*
  - *Somatic cell mutagenicity tests in vivo, in mammals; or*
  - *Other in vivo somatic cell genotoxicity tests which are supported by positive results from in vitro mutagenicity assays* (ECHA, 2015).

As criteria for category 2 are not applicable, also category 1 may not be assigned. Tris(2-methoxyethoxy)-vinylsilane does not fulfil the criteria for germ cell mutagenicity (Category 1 or Category 2), as described in ECHA (2015).

However, according to the criteria also data on similar substances, which are germ cell mutagens shall be considered:

- *Substances which are positive in in vitro mammalian mutagenicity assays, and which also show chemical structure activity relationship to known germ cell mutagens, shall be considered for classification as Category 2 mutagens (*ECHA, 2015)

Both criteria are not relevant for tris(2-methoxyethoxy)-vinylsilane: 1) the substance is negative in mammalian mutagenicity assays, 2) the presumed metabolite, 2-methoxyethanol, is not a known germ cell mutagen. Although there has been some suggestions of an induction of genetic effects in male germ cells for 2-methoxyethanol, the results from these studies are inconclusive (WHO, 2009). Also, the German commission for biological exposure limits summarises: "*the majority of in vitro investigations and animal studies do not indicate genotoxic effects or germ cell toxicity for 2-methoxyethanol*" (Drexler and Hartwig, 2009). In agreement with this evaluation, the substance does not have a harmonised classification according to CLP Regulation (EC) No. 1272/2008 (Annex VI) for this endpoint. Thus, data on 2-methoxyethanol cannot be used to support classification of tris(2-methoxyethoxy)-vinylsilane for germ cell mutagenicity.

10.8.3 Conclusion on classification and labelling for germ cell mutagenicity

Data are conclusive but not sufficient for classification.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

Tris(2-methoxyethoxy)vinylsilane was negative in three reverse bacterial mutation assays (Ames assays), in one mammalian chromosome aberration test in vitro on Chinese hamster ovary cells and in one mammalian cell gene mutation test with mouse lymphoma L5178Y cells. All the tests were performed according to Good Laboratory Practices (GLP), followed OECD test guidelines (TG) or were of acceptable quality.

The Dossier Submitter (DS) noted that ambiguous effects with respect to germ cell mutagenicity have been observed with the substance 2-methoxyethanol (WHO, 2009), which is a probable metabolite of tris(2-methoxyethoxy)vinylsilane. 2-Methoxyethanol does not induce gene mutations in *in vitro* investigations. However, there is some indication that it induces clastogenic damage and there is consistent evidence that the initial metabolite 2-methoxyacetaldehyde (MALD) is genotoxic *in vitro* in several cell lines. Results of the available *in vivo* studies suggest that 2-methoxyethanol is not genotoxic in somatic cells. Although there has been some suggestions of an induction of genetic effects in male germ cells, the results from these studies are inconclusive (WHO, 2009). Also, the Drexler and Hartwig, 2009 considered that the majority of in vitro investigations and animal studies do not indicate genotoxic effects or germ cell toxicity for 2-methoxyethanol. In agreement with this evaluation, the substance does not have a harmonised classification according to CLP Regulation (EC) No. 1272/2008 (Annex VI) for this endpoint.

Based on these data, the DS concluded that tris(2-methoxyethoxy)vinylsilane does not warrant classification for germ cell mutagenicity.

Comments received during public consultation

Three Member States Competent Authorities (MSCAs) supported no classification of

Tris(2-methoxyethoxy)vinylsilane as a germ cell mutagen.

Assessment and comparison with the classification criteria

According to Annex VI of the CLP regulation, classification in germ cell mutagenicity Category 2 is based on "positive evidence obtained from experiments in mammals and/or in some cases from in vitro experiments, obtained from:
- Somatic cell mutagenicity tests *in vivo*, in mammals; or
- Other *in vivo* somatic genotoxicity tests which are supported by positive results from *in vitro* mutagenicity assay"

Taking into account negative results in several *in vitro* studies, RAC is of the opinion that tris(2-methoxyethoxy)vinylsilane does not warrant classification for germ cell mutagenicity.

10.9 Carcinogenicity

No data avaialble

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

No data available

10.9.2 Comparison with the CLP criteria

There are not sufficient data to assess carcinogenicity of tris(2-methoxyethoxy)-vinylsilane. From data on genotoxicity, there are no indications of a potential carcinogenic effect. For 2-methoxyethanol, a known hydrolysis product and assumed metabolite of tris(2-methoxyethoxy)-vinylsilane, no suitable studies to assess carcinogenicity are available (WHO, 2009).

10.9.3 Conclusion on classification and labelling for carcinogenicity

Due to insufficient data classification of tris(2-methoxyethoxy)-vinylsilane with regard to carcinogenicity is not possible.

10.10 Reproductive toxicity

10.10.1 Adverse effects on sexual function and fertility

Table 10: Summary table of animal studies on adverse effects on sexual function and fertility

Method, guideline	**Test substance, species, strain, sex, no/group, dose levels, duration of exposure**	**Results (sexual function and fertility)**		**Reference**
		Male (Parental)	**Female (Parental)** **(reproductive phase females)***	

OECD TG 422 (Combined repeated dose toxicity study with the reproductive reproduction/ developmental toxicity sreening test) GLP; Reliability: 1 (reliable without restriction), according to (ECHA, 2017b)	tris(2-methoxyethoxy)vinylsilane, purity is confidential information gavage (vehicle: dehydrated, deacidified corn oil), -rat Crl: CD(SD) - IGS BR male/female N= 10/sex/group 0, 25, 75, and 250 mg/kg bw/d Exposure duration: Males & toxicity phase females *: 28d; 14 days prior to mating; continuing throughout mating Females (reproductive phase *): 14 days prior to mating; throughout mating and gestation and continuing through lactation day 3	<u>250 mg/kg bw/d:</u> Small and/or soft testes and/or epididymides Reproductive performance effects (male fertility index): 60 % vs. control 90 % Mean number of days between pairing and coitus increased. 9 of 10 females with evidence of mating. Mean absolute and relative testes and epididymal weights reduced Microscopally, small/soft testes correlated with seminiferous tubule degeneration in all males Hypospermia and luminal cellular debris in epididymides (secondary to loss of spermatogenesis in testes) Mean absolute and relative prostate weights reduced. Reduction correlated microscopically with decreased secretion and/or atrophy Mean absolute and relative seminal vesicle weights reduced with no micro-scopic findings	<u>250 mg/kg bw/d:</u> Mean gestation body weight gains reduced (22.1 % lower at gd 20), attributed to resorbed litters Reproductive performance effects (female fertility index): 60 % vs. control 90 % Mean number of days between pairing and coitus increased. 9 of 10 females with evidence of mating. Mean gestation length increased in the single female that delivered 3/9 reproductive phase females mated non-gravide 5/9 entirely resorbed litters	(OECD, 2006), (ECHA, 2017b)
		<u>75 mg/kg bw/d:</u> mean absolute and relative prostate weights reduced. Reduction correlated microscopically with decreased secretion and/or atrophy	<u>75 mg/kg bw/d:</u> 1 reproductive phase moribund female euthanised in extremis, probably due to dystocia (gd 22) Mean gestation length increased	
		<u>25 mg/kg bw/d:</u> NOAEL	<u>25 mg/kg bw/d:</u> NOAEL	

		Results (general health endpoints, not reproduction)		
		Male (Parental)	**Female (Parental)** **(toxicity phase females) ***	
		<u>250 mg/kg bw/d</u>	<u>250 mg/kg bw/d</u>	

		Food consumption reduced (day 14-28), 6.7 % mean body weight vs. control at day 28; Haematological changes; hypocellularity in sternal bone marrow, aggregates of mature granulocytes absent Increased albumin/globulin ratios Mean abs. and relative thymus weights reduced, correlated to microscopic findings of lymphoid depletion. Small thymus Mean abs. and relative adrenal gland weights reduced, no microscopic correlate Adhesion and/or white areas on the spleen; corresponding with capsular fibrosis	Haematological changes; hypocellularity in sternal bone marrow, aggregates of mature granulocytes absent Increased albumin/globulin ratios Mean abs. and relative thymus weights reduced, correlated to microscopic findings of lymphoid depletion. Small thymus (temporarily) Mean abs. and relative adreanal gland weights reduced, no microscopic correlate (temporarily) Adhesion and/or white areas on the spleen; corresponding with capsular fibrosis	
		<u>75 mg/kg bw/d</u> Adhesion and/or white areas on the spleen; corresponding with capsular fibrosis	<u>75 mg/kg bw/d</u> NOAEL	
		<u>25 mg/kg bw/d</u> NOAEL		

* For details on the study design see Annex I to this report.

There were no clinical findings reported in males and females of the toxicity phase and all survived until study termination up to 250 mg/kg bw/d. There were no test article-related effects observed at the functional observation box (FOB) or locomotor activity evaluations in the males or toxicity phase females at any dose level. In the high dose males food consumption was reduced in the first week of dosing, bw gain was lowered in the third and fourth week and on day 28 body weight was 6.7% lower than in control males. These parameters were not affected in females of the toxicity phase. Body weight gain and food consumption (only during gestation but not during the premating phase) was reduced in reproductive phase females and gd20 body weight 22.1% lower than in control dams. The latter finding was attributed to total resorption in five of nine dams.

From this study, a NOAEL of 25 mg/kg bw/d is derived for reproductive effects (male and female sexual function and fertility). Some of the reproductive effects (resorbed litters) may, in fact, be linked to reproductive effects on the dams or on the male parent animals or may indicate developmental effect (see section 10.10.4). General health effects on parental animals (other than reproductive toxicity endpoints) were observed at 250 mg/kg bw/d (female rats) and at 75 and 250 mg/kg bw/d (male rats) with a NOAEL of 75 mg/kg bw/d (females) and a NOAEL of 25 mg/kg bw/d (males).

No access to the original study was available, but based on the available information this OECD guideline 422 study is considered reliable (with some uncertainties due to limited reporting), in agreement with the reliability assessment by the registrant (“reliable without restrictions”, reliablility: 1).

Table 11: Summary table of other studies relevant for toxicity on sexual function and fertility

Method, guideline	Test substance, species, strain, sex, no/group, dose levels, duration of exposure	Results (sexual function and fertility)	Reference
Subacute rat study on mating performance and epididymal sperm parameters, no guideline study	2-methoxyethanol (no information on purity available), destilled water solution per os; 0, 50, 100, 200 mg/kg bw/d; 5 days; n = 20/group thereafter mated with untreated females (n = 40/group)	At 200 mg/kg bw/d reduced fertility (males) ; 200 and 100 mg/kg bw/d: widespread testicular damage; elevations of abnormal sperm forms in epididymis; very mild testicular effects at 50 mg/kg bw/d. Percentage of females found pregnant after mating and number of live fetuses per pregnant female after mating with exposed males reduced at 200 mg/kg bw/d and 100 mg/kg bw/d, not at 50 mg/kg bw/d. Resorptions and total number corpora lutea minus total implantation sites per fermale significantly elevated at 200 mg/kg bw/d.	(Chapin et al., 1985)

2-Methoxyethanol is a hydrolysis product and assumed metabolite of tris(2-methoxyethoxy)vinylsilane. Data as reported in Table 11 demonstrate toxicity on sexual function and fertility of 2-methoxyethanol with a NOAEL of 50 mg/kg bw/d for effects on females (percentage of females found pregnant after mating and number of live fetuses per pregnant female after mating with exposed males reduced). For effects on males a LOAEL can be derived based on very mild testicular effects seen at 50 mg/kg bw/day.

10.10.2 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

The OECD Guideline 422 study on tris(2-methoxyethoxy)vinylsilane, as reported in Table 10, provides clear evidence effects on reproduction (effects on sexual function and fertility) in male and in female rats as demonstrated by, e.g., reduced fertility index, seminiferous tubule degeneration, hypospermia and prostate atrophy (males) or reduced fertility and changes in gestational length (females). The NOAEL for reproductive effects (25 mg/kg bw/d) is equal or lower than the NOAEL for other systemic endpoints (75 mg/kg bw/d, females; 25 mg/kg bw/d, males) and reproductive toxicity does not appear to be unspecific or secondary effects from general toxicity. In males, effects reported (apart from those on on sexual function) at 75 mg/kg/d were described as: “adhesion and/or white areas on the spleen”. At this dose sexual function was already significantly impaired (“mean absolute and relative prostate weights reduced. Reduction correlated microscopically with decreased secretion and/or atrophy”), which cannot be regarded as a secondary effect to toxicity in the spleen. In females the NOAEL for other but reproductive toxicity was 75 mg/kg/d. At this dose mean gestation length was increased and there was one probable case of dystocia on gd22. The single female that delivered in the high dose also had an increased gestation length, further giving support to this finding in the mid dose.

In addition, similar effects have been observed from exposure of rats to 2-methoxyethanol in numerous experimental studies (WHO, 2009). 2-Methoxyethanol is an assumed metabolite of tris(2-methoxyethoxy)vinylsilane, formed by hydrolysis. The study by Chapin et al. (1985) on 2-methoxyethanol is not fully comparable with the study design used for tris(2-methoxyethoxy)vinylsilane. However, as the study also is performed with oral exposure of rats, is directed to analyse male fertility and reproductive outcome and is used as a supportive study in REACH registration for reproductive toxicity of 2-methoxyethanol (reliablility: 2, reliable with restrictions according to the Registrant) it is regarded as “a useful contribution to weight of evidence” and was selected and reported in Table 11. The study provides supportive evidence that tris(2-methoxyethoxy)vinylsilane causes reproductive effects, although quantitative conclusions (compatibility of effect doses for tris(2-methoxyethoxy)vinylsilane and for 2-methoxyethanol) cannot be provided. As no *in vivo* studies on toxicokinetics of tris(2-methoxyethoxy)vinylsilane exist, attributing quantitative fractions to the 2-methoxyethanol metabolic pathway, only qualitative compatibility can be

confirmed. However, it is not unambiguously shown that 2-methoxyethanol is the (sole) critical metabolite responsible for the observed effects.

10.10.3 Comparison with the CLP criteria

The criteria for classification as toxic to reproduction, fertility are defined in the ECHA guidance (ECHA, 2015) as follows:

- Adverse effects on sexual function and fertility are described as *"any effect of substances that has the potential to interfere with sexual function and fertility. This includes, but is not limited to, alterations to the female and male reproductive system, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behaviour, fertility, parturition, pregnancy outcomes, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive systems… Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects".*
- Regarding the relevance of such "other toxic effects" ECHA explains: *"There is no established relationship between fertility effects and less marked systemic toxicity. Therefore it should be assumed that effects on fertility seen at dose levels causing less marked systemic toxicity are not a secondary consequence of this toxicity."*

For tris(2-methoxyethoxy)vinylsilane, adverse effects on sexual function and fertility (Table 10) were observed in males and females at a dose without the observation of other toxic effects that could be causally linked with the observed reproductive toxicity (75 mg/kg bw/d). No parental toxicity apart from slight changes in the spleen seen in males was observerd at that dose. Though at the dose of 250 mg/kg bw/day haematology, bone marrow, thymus, lymph nodes and organ weights (thymus, adrenal) were affected and no detailed information on the degree of these findings can be derived from the registration dossier, it can be concluded that the severe reproductive toxicity (e.g. fertility impairment) observed at 250 mg/kg bw/d is not to be regarded as secondary effect. There were no clinical findings reported in toxicity phase males and females up to 250 mg/kg bw/day and no or only minor effects on food consumption, final body weight and body weight gain, except for the body weight of females on gd 20 (reduced by 22.1% compared to controls) which was attributed to total resorption in five of nine dams.Clear evidence of an adverse effect on sexual function and fertility is given, e.g., by seminiferous tubule degeneration (all males, high dose), hypospermia (high dose males) and prostate atrophy (mid and high dose males) or changes in gestational length (mid and high dose females) and reduced fertility index (high dose males and females, 60% vs. 90% in controls).

Tris(2-methoxyethoxy)vinylsilane should be classified: Category 1B, presumed human reproductive toxicant.

This conclusion is based on observations regarding "sexual function and fertility" and, as such, results in a Hazard statement H360F, not precluding a similar or identical classification because of developmental effects (i.e., H360D; Sections 10.10.4-10.10.6).

The classification is independent from the occurrence of 2-methoxyethanol as an impurity, because it may reasonably be assumed that the hydrolysis product 2-methoxyethanol is a metabolite of tris(2-methoxyethoxy)vinylsilane. Therefore, if 2-methoxyethanol is determining the reproductive effects of tris(2-methoxyethoxy)vinylsilane, it will be bioavailable and may cause such health effects, regardless whether it is also present as an impurity or not.

2-Methoxyethanol is a classified Repr. 1B (H360FD) substance. Therefore the presence of this substance as an assumed metabolite provides supportive evidence for this classification on sexual function and fertility of tris(2-methoxyethoxy)vinylsilane.

10.10.4 Adverse effects on development

Table 12: Summary table of animal studies on adverse effects on development

Method, guideline	Test substance, species, strain, sex, no/group, dose levels, duration of exposure	Results (developmental), observations in fetuses and pups	Reference
OECD Guideline 422 (Combined repeated dose toxicity study with reproduction/ developmental toxicity sreening test) GLP; Reliability: 1 (reliable without restriction), according to (ECHA, 2017b)	tris(2-methoxyethoxy)vinylsilane, purity is confidential information gavage (vehicle: dehydrated, deacidified corn oil), -rat Crl: CD(SD) - IGS BR male/female N = 10/sex/group 0, 25, 75, and 250 mg/kg bw/d Exposure duration: Males & toxicity phase females *: 28 d; 14 days prior to mating; continuing throughout mating Reproductive phase females *: 14 days prior to mating; throughout mating and gestation and continuing through lactation day 3	<u>250 mg/kg bw/d:</u> 5/9 entirely resorbed litters total litter loss for 1/9 female gravid at lactation day 0 <u>75 mg/kg bw/d:</u> postnatal survival reduced throughout lactation period (ld: 1-4), primarily due to: Total litter loss at lactation day 2 (1 female) Mean number of pups born and life litter size on PND 0 reduced (slight increase in number of pups dead, missing and presumed cannabalized) Mean number of implantation sites reduced, number of unaccounted for implantation sites increased. <u>25 mg/kg bw/d:</u> NOAEL **Results: effects on dams (general health endpoints and maternal)** <u>250 mg/kg bw/d:</u> Mean gestation body weight gains reduced (22.1 % lower at gd 20), attributed resorbed litters Haematological changes; hypocellularity in sternal bone marrow, aggregates of mature granulocytes absent Increased albumin/globulin ratios Mean relative abs. and relative thymus weights reduced, correlated to microscopic findings of lymphoid depletion Small thymus (temporarily) Mean abs. and relative adreanal gland weights reduced, no microscopic correlate (temporarily) <u>75 mg/kg bw/d:</u> NOAEL	(OECD, 2006), (ECHA, 2017b)

* For details on the study design see Annex I to this report.

From this study, a NOAEL of 25 mg/kg bw/d is derived for reproductive toxicity effects (developmental toxicity). No gross pathology findings in offsprings in all exposure groups and control were detected. Other health effects on parental animals (other than reproductive toxicity endpoints) were observed at 250 mg/kg bw/d in females and at 75 and 250 mg/kg bw/d in males with a NOAEL of 75 mg/kg bw/d (maternal effects).

No access to the original study was available, but based on the available information this OECD guideline 422 study is considered reliable (with some uncertainties due to limited reporting), in agreement with the

reliability assessment by the registrant ("reliable without restrictions", reliablility: 1). No further information on actual figures available.

Table 13: Summary table of other studies relevant for developmental toxicity

Method, guideline	Test substance, species, strain, sex, no/group, dose levels, duration of exposure	Observations (embyo- and fetotoxic effects, for litters, which survived to term)	Reference
Developmental toxicity study. No guideline study, but equivalent or similar to OECD TG 414 according to Registrant (ECHA, 2017b)	2-methoxyethanol (no information on purity available), oral exposure (substance in destilled water per os), application: gestation day 7-18; female Sprague-Dawley rats; Approx. daily doses: 0, 16, 31, 73 mg/kg bw/d; N = 10 dams/group	73 mg/kg bw/d: dead/resorbed: 92 % survivors malformed (4/10 fetuses = 40 %)	(Nelson et al., 1989)
		31 mg/kg bw/d: dead/resorbed: 14 % survivors malformed (6/145 fetuses = 4 %)	
		16 mg/kg bw/d: dead/resorbed: 7 % survivors malformed: 0 %	
		0 mg/kg bw/d: dead/resorbed: 11 % survivors malformed: 0 %	
		16 mg/kg bw/d: NOAEL	

2-Methoxyethanol is a hydrolysis product and assumed metabolite of tris(2-methoxyethoxy)vinylsilane. Data as reported in Table 13 demonstrate developmental toxicity of 2-methoxyethanol with a NOAEL of 16 mg/kg bw/d. The maternal NOAEL in this study was 73 mg/kg bw/d (reduced weight gain) with other maternal effects only above 140 mg/kg bw/d. Terata consist of visceral (cardiovascular) and skeletal (fused ribs, rudimentary 14th ribs, missing vertebrae) malformations.

10.10.5 Short summary and overall relevance of the provided information on adverse effects on development

Exposure of pregnant rats to tris(2-methoxyethoxy)vinylsilane leads to increased resorptions, litter losses and reduced implantations (Table 12). These endpoints affect the developing life and therefore are regarded as developmental effects. However, such effects may be secondary to impairments of the reproductive integrity of the dams (effects on sexual function and fertility) or even indirect effect on female fertility induced by reproductive toxicity to the mating males (see effects on untreated females after exposure of males to 2-methoxyethanol, as documented in Table 11). There have been no adequate examinations on (skeletal or visceral) malformations on the fetus or postpartum. This uncertainty is due to the screening type of the study design (OECD guideline 422). No adequate study according to OECD TG 414 is available (see Section 3).

The nature of the observed reproductive effects as developmental effects is supported by respective observations on 2-methoxyethanol. Developmental effects have been observed from exposure of rats to 2-methoxyethanol in numerous experimental studies (WHO, 2009). The study by Nelson et al. (1989) on 2-methoxyethanol is not comparable with the study design used for tris(2-methoxyethoxy)vinylsilane. However, as the study also is performed with oral exposure of rats and is directed to analyse developmental effects and is used as a key study in the REACH registration dossier for developmental toxicity of 2-methoxyethanol (according to the Registrant: reliablility: 2, reliable with restrictions), it was selected and reported in Table 13. The study provides supportive evidence for classifying tris(2-methoxyethoxy)vinylsilane, although quantitative conclusions (compatibility of effect doses for tris(2-methoxyethoxy)vinylsilane and for 2-methoxyethanol) cannot be provided. As no *in vivo* studies on

toxicokinetics of tris(2-methoxyethoxy)vinylsilane exist, attributing quantitative fractions to the 2-methoxyethanol metabolic pathway, only qualitative compatibility can be confirmed. However, it is not unambiguously shown that 2-methoxyethanol is the (sole) critical metabolite responsible for the observed effects.

10.10.6 Comparison with the CLP criteria

The CLP criteria for classification as toxic to reproduction, development are specified in the ECHA guidance (ECHA, 2015) as follows:

- *For pragmatic purposes of classification, developmental toxicity essentially means adverse effects induced during pregnancy, or as a result of parental exposure. These effects can be manifested at any point in the life span of the organism. The major manifestations of developmental toxicity include (1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) functional deficiency.*

Tris(2-methoxyethoxy)vinylsilane leads to developmental toxicity as documented in Table 12. For example, at 250 mg/kg/d entirely resorbed litters were observed and at 75 mg/kg/d postnatal survival was reduced. These effects are in compliance with the ECHA definition of developmental toxicity.

However, the guidance (ECHA, 2015) emphasises the potential influence of maternal toxicity on the developmental outcome:

- *Development of the offspring throughout gestation and during the early postnatal stages can be influenced by toxic effects in the mother either through non-specific mechanisms related to stress and the disruption of maternal homeostasis, or by specific maternally-mediated mechanisms. In the interpretation of the developmental outcome to decide classification for developmental effects it is important to consider the possible influence of maternal toxicity. This is a complex issue because of uncertainties surrounding the relationship between maternal toxicity and developmental outcome. Expert judgement and a weight of evidence approach, using all available studies, shall be used to determine the degree of influence that shall be attributed to maternal toxicity when interpreting the criteria for classification for developmental effects. The adverse effects in the embryo/foetus shall be first considered, and then maternal toxicity, along with any other factors which are likely to have influenced these effects, as weight of evidence, to help reach a conclusion about classification ().*

For tris(2-methoxyethoxy)vinylsilane, adverse effects on development (Table 12) were observed at a dose without other toxic effects in dams (75 mg/kg/d). Therefore, developmental effects at the higher dose (e.g., resorption) are not regarded to be the consequence of maternal toxicity.

Moreover, ECHA explains:

- *Developmental effects which occur even in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be unequivocally demonstrated on a case-by-case basis that the developmental effects are secondary to maternal toxicity* (ECHA, 2015).

There are no unambiguous reasons, even at 250 mg/kg/d, to assume that the developmental effects of tris(2-methoxyethoxy)vinylsilane are secondary to maternal toxicity.

However, even if maternal toxicity is not regarded relevant for the developmental effects observed, observed embryotoxic effects are not unambiguously linked to a *direct* impact on development, but could be secondary to effects on sexual function and fertility on the parent animals. But the ECHA guidance (ECHA, 2015) defines developmental toxicity in a broad sense, with "*any effect that interferes with normal development of the conceptus, either before or after birth, and resulting from exposure to either parent prior to conception, or exposure of the developing offspring during prenatal development*" as a developmental toxicant, specifically including "death of the developing organism" (ECHA, 2015). Even though "*some reproductive toxic effects cannot be clearly assigned to either impairment of sexual function and fertility or to developmental toxicity*" the given definition for developmental toxicity leads to the classification of tris(2-methoxyethoxy)vinylsilane as a developmental toxicant.

Therefore tris(2-methoxyethoxy)vinylsilane is to be classified: Category 1B, presumed human reproductive

toxicant.

This conclusion is based on observations regarding “developmental toxicity” and, as such, results in a Hazard statement H360D, not precluding a similar or identical classification due to effects on fertility and sexual function (i.e., H360F; Sections 10.10.1 - 10.10.3).

The classification is independent from the occurrence of 2-methoxyethanol as an impurity, because it may reasonably be assumed that the hydrolysis product 2-methoxyethanol is a metabolite of tris(2-methoxyethoxy)vinylsilane. Therefore, if 2-methoxyethanol is determining the reproductive effects of tris(2-methoxyethoxy)vinylsilane, it will be bioavailable and may cause such health effects, regardless whether it is also present as an impurity or not.

2-Methoxyethanol is a classified Repr. 1B (H360FD) substance. Therefore the presence of this substance as an assumed metabolite provides supportive evidence for this classification of tris(2-methoxyethoxy)vinylsilane.

10.10.7 Adverse effects on or via lactation

No data available

10.10.8 Short summary and overall relevance of the provided information on effects on or via lactation

No data available

10.10.9 Comparison with the CLP criteria

Not applicable

10.10.10 Conclusion on classification and labelling for reproductive toxicity

The results from experimental animal testing (OECD guideline 422) on tris(2-methoxyethoxy)vinylsilane provide clear evidence of an adverse effect on sexual function and fertility. As far as “occurring together with other toxic effects, the adverse effect on reproduction is considered not to be a secondary nonspecific consequence of other toxic effects” (ECHA, 2015). Clear evidence of an adverse effect on sexual function and fertility is given, e.g., by seminiferous tubule degeneration, hypospermia and prostate atrophy (males) or reduced fertility, changes in gestational length (females) and reduced fertility index (males and females).

ECHA (2015) states, that “effects on fertility seen at dose levels causing less marked systemic toxicity are not a secondary consequence of this toxicity”. This is the case for the observations made with tris(2-methoxyethoxy)vinylsilane exposure in the OECD guideline 422 study.

Therefore tris(2-methoxyethoxy)vinylsilane is to be classified: Category 1B, presumed human reproductive toxicant.

The results from experimental animal testing (OECD guideline 422) on tris(2-methoxyethoxy)vinylsilane provide clear evidence of an adverse effect on development. As far as “occurring together with other toxic effects, the adverse effect on reproduction is considered not to be a secondary nonspecific consequence of other toxic effects” (ECHA, 2015).

The observed embryotoxic effects are clear signs of developmental toxicity in a broad sense, which is defined as “any effect that interferes with normal development of the conceptus, either before or after birth, and resulting from exposure to either parent prior to conception, or exposure of the devoping offspring during prenatal development.”, specifically including “death of the developing organism” (ECHA, 2015).

Therefore tris(2-methoxyethoxy)vinylsilane is to be classified: Category 1B, presumed human reproductive toxicant.

Therefore, overall, tris(2-methoxyethoxy)vinylsilane should be classified as Repr. 1B, presumed human reproductive toxicant and the assigned Hazard Statement is H360FD "May damage fertility. May damage the unborn child".

The classification is independent from the occurrence of 2-methoxyethanol as an impurity, because it may reasonably be assumed that the hydrolysis product 2-methoxyethanol is a metabolite of tris(2-methoxyethoxy)vinylsilane. Therefore, if 2-methoxyethanol is determining the reproductive effects of tris(2-methoxyethoxy)vinylsilane, it will be bioavailable and may cause such health effects, regardless whether it is also present as an impurity or not.

2-methoxyethanol is a classified Repr. 1B (H360FD) substance. Therefore the presence of this substance as an assumed metabolite provides supportive evidence for this classification of tris(2-methoxyethoxy)vinylsilane.

There were no data to assess potential effects on or via lactation.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

The potential adverse effects of tris(2-methoxyethoxy)vinylsilane on sexual function and fertility and on development were assessed based on results of a combined oral repeated dose toxicity study with the reproduction/developmental toxicity screening test performed according to OECD TG 422 and performed under GLP. In this study, CD(SD) rats (10/sex/group) were given 0, 25, 175 and 250mg/kg bw/d by gavage. Males were exposed to tris(2-methoxyethoxy)vinylsilane during 14 days prior to mating and throughout the mating period of 14 days. Females were exposed to the test substance during the toxicity phase of 28 days. In the reproductive screening phase, other groups of females were administered tris(2-methoxyethoxy)vinylsilane by gavage daily for a minimum of 14 days prior to mating, throughout mating and gestation and continuing through lactation day 3. Since the original study report was not available to the DS, qualitative descriptions of results were taken by the DS from the Reach registration section of the ECHA dissemination website.

According to the DS, exposure to tris(2-methoxyethoxy)vinylsilane did not result in marked systemic toxicity at any dose level. There were no clinical findings reported in males and females during the toxicity phase and all animals survived until study termination up to 250 mg/kg bw/d. There were no test article-related effects observed at the functional observation battery (FOB) or locomotor activity evaluations in the males or during the toxicity phase of the females at any dose level. In the high dose males, food consumption was reduced in the first week of dosing, body weight gain was lowered in the third and fourth week and on day 28 body weight was 6.7% lower than in control males. These parameters were not affected in females during the toxicity phase. Body weight gain and food consumption (only during gestation but not during the premating phase) was reduced in the reproductive screening phase, treated females at GD20 had a mean body weight 22.1% lower than in control dams. The latter finding was attributed to total resorption in five of nine dams.

Effect on sexual function and fertility

According to the DS, the study provided evidence of adverse effects on reproduction in male and in female rats as demonstrated by, e.g., reduced fertility index, seminiferous tubule degeneration, hypospermia and prostate atrophy (males) or reduced fertility and changes in gestational length (females).

At a dose of 250 mg/kg bw in males, the following effects were observed: the mean number of days between pairing and coitus was increased; the mean absolute and relative testes and epididymal weights were reduced; microscopally, small/soft testes correlated with seminiferous tubule degeneration in all males; hypospermia and luminal cellular debris in epididymides (secondary to loss of spermatogenesis in testes); mean absolute and relative prostate weights were reduced. In females exposed at a dose of 250 mg/kg/d, 9 of 10 females were with evidence of mating, but fertility index was 60% *vs*. 90% in the control group. In addition, 3 out of 9 reproductive screening phase females mated were found non-gravidae and the mean gestation length was increased in the single female that delivered.

At a dose of 75 mg/kg in males, mean absolute and relative prostate weights were reduced. This reduction correlated microscopically with decreased secretion and/or atrophy of the prostate. In females, the mean gestation length was increased, and 1 moribund female was euthanised in extremis, probably due to dystocia (GD 22).

The NOAEL for reproductive effects (25 mg/kg bw/d) is equal or lower than the NOAEL for other systemic endpoints (75 mg/kg bw/d in females; 25 mg/kg bw/d in males). The reproductive toxicity does not appear to be unspecific or secondary effects from general toxicity.

The DS also reported similar effects observed from exposure of rats to 2-methoxyethanol in numerous experimental studies (WHO, 2009). 2-Methoxyethanol is an assumed metabolite of tris(2-methoxyethoxy)vinylsilane, formed by hydrolysis. In the subacute rat oral toxicity study by Chapin *et al.* (1985), 2-methoxyethanol caused reduced fertility in males at a dose level of 200 mg/kg/d. At dose levels of 200 and 100 mg/kg bw/d, 2-methoxyethanol produced widespread testicular damage and elevations of abnormal sperm forms in epididymis. At 50 mg/kg bw/d, very mild testicular effects at 50 mg/kg bw/d were observed. Percentage of females found pregnant after mating and number of live fetuses per pregnant female after mating with exposed males was reduced at 200 mg/kg bw/d and 100 mg/kg bw/d, but not at 50 mg/kg bw/d.

According to the DS, the study of Chapin *et al.* (1985) with 2-methoxyethanol provides supportive evidence that tris(2-methoxyethoxy)vinylsilane causes reproductive effects, although quantitative conclusions (compatibility of effect doses for tris(2-methoxyethoxy)vinylsilane and for 2-methoxyethanol) cannot be provided.

Based on the above data, the DS proposed to classify tris(2-methoxyethoxy)vinylsilane as Repr. 1B; H360F (May damage fertility).

Developmental toxicity

Developmental toxicity was assessed by the DS based on effects observed in the combined oral repeated dose toxicity study with the reproduction/developmental toxicity

screening test in rats described above.

At a dose level of 250 mg/kg/d, in 5 out of 9 females the litters were entirely resorbed and total litter loss was observed in 1 out of 9 pregnant females at lactation day 0. The number of resorptions and total number of preimplantation loss per female was significantly elevated.

At a dose level of 75 kg/kg/d postnatal survival was reduced shortly after birth due to:

- total litter loss in 1 female at lactation day 2
- mean number of pups born and alive on PND 0 was reduced (due to slight increase in number of pups dead, missing and presumed cannibalised)
- mean number of implantation sites reduced,
- number of unaccounted for implantation sites increased, which most probably was due to increased number of preimplantation loss.

No developmental effects were found at dose of 25 mg/kg/d.

In summary, exposure to tris(2-methoxyethoxy)vinylsilane during pregnancy of rats leads to increased resorptions, litter losses and reduced implantations at doses not causing a marked maternal toxicity. There have been no adequate examinations on (skeletal or visceral) malformations on the fetus or postpartum. This uncertainty is due to the screening type of the study design (OECD guideline 422). No adequate study according to OECD TG 414 is available.

According to the DS, it is known that 2-methoxyethanol is a developmental toxicant classified as Repr. 1B; H360FD. Developmental effects have been observed from exposure of rats to 2-methoxyethanol in numerous experimental studies (WHO, 2009). The study by Nelson *et al*. (1989) on 2-methoxyethanol is used as a key study in the REACH registration dossier to demonstrate the developmental toxicity of 2-methoxyethanol.
Based on the above data DS proposed to classify tris(2-methoxyethoxy)vinylsilane as Repr. 1B; H360D May damage the unborn child

Comments received during public consultation

Three MSCAs supported classification of tris(2-methoxyethoxy)vinylsilane as Repr. 1B; H360FD.

Assessment and comparison with the classification criteria

Classification as Repr. 1A is not warranted because of the lack of human data..

Sexual Function and Fertility

Regarding adverse effects on reproductive function and fertility, in the rat combined oral repeated dose toxicity study with the reproduction/developmental toxicity screening test there were clear treatment-related adverse effects on fertility or reproductive performance from a dose level of 75 mg/kg bw/day. RAC agrees with the DS that the study provided clear evidence of adverse effects on reproduction in male and in female

rats as demonstrated by reduced fertility index, seminiferous tubule degeneration, hypospermia and prostate atrophy (males) or reduced fertility and changes in gestational length (females).

The same study also provided clear evidence for significant developmental effects associated with tris(2-methoxyethoxy)vinylsilane from a dose level of 75 mg/kg bw/day. There was no indication of malformations but the number of resorptions and the total number of preimplantation loss per female was significantly elevated.

In conclusion, taking into account the clear evidence derived from an acceptable animal study that tris(2-methoxyethoxy)vinylsilane is affecting spermatogenesis, reduces the fertility index, leads to increased preimplantation loss, increased intrauterine deaths of embryo and foetuses, increased mortality of newborn rats shortly after birth at dose levels not causing marked parental toxicity, RAC agrees with the DS that tris(2-methoxyethoxy)vinylsilane warrants classification as Repr. 1B; H360FD (May damage fertility; may damage the unborn child). Such classification is further supported by the fact that 2-methoxyethanol, a product of tris(2-methoxyethoxy)vinylsilane hydrolysis, and a presumed metabolite of tris(2-methoxyethoxy)vinylsilane in mammals is a known reproductive toxicant with harmonised classification as Repr. 1B; H360FD.

10.11 Specific target organ toxicity-single exposure

Evaluation not performed for this substance

10.12 Specific target organ toxicity-repeated exposure

Evaluation not performed for this substance

Part of the data presented in Table 10 and Table 12 were taken from the dissemination database, chapter "repeated dose toxicity oral". The study was performed according to OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test).

10.13 Aspiration hazard

Evaluation not performed for this substance

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Evaluation not performed for this substance

12 EVALUATION OF ADDITIONAL HAZARDS

Evaluation not performed for this substance

13 ADDITIONAL LABELLING

Not applicable

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15 ANNEXES

Annex I: Confidential or non-confidential annex documenting the key study for assessment of reproductive toxicity (OECD TG 422- study).