LATVIJAS VIDES, ĢEOLOĢIJAS UN METEOROLOĢIJAS CENTRS

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Vinyl acetate

EC No 203-545-4

CAS No 108-05-4

Evaluating Member State(s): Latvia

Dated: 1 October 2020

Template Version 2.1
March 2015

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2019

Member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

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 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

Vinyl acetate was originally selected for substance evaluation in order to clarify concerns about:

- Suspected reprotoxic;

- Potential endocrine disruptor;

- Suspected sensitiser;

- Consumer use;

- Wide dispersive use;

- High (aggregated) tonnage.

During the evaluation additional concerns were not identified.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Several processes on vinyl acetate are ongoing or have been completed:

- Harmonised Classification and Labelling (Annex VI of CLP Regulation section 3.1.);
- Seveso III Directive (Directive 2012/18/EU which repeals the Seveso II Directive 96/82/EC), Category P5a, P5b, P5c;
- A Decision on a compliance check (CCH-D-2114355769-31-01/F) to request further information was issued on 30 March 2017 in order to submit:
    - an in vivo mammalian comet assay study (OECD TG 489) in accordance with Column 2 of Section 8.4. of Annex X of the REACH Regulation, including 'modified experimental conditions that enable the detection of DNA crosslinks'; and
    - a pre-natal developmental toxicity study in a second species (OECD TG 414) in accordance with Section 8.7.2. of Annex X of the REACH Regulation.

  This compliance check decision has been partly withdrawn by ECHA Board of Appeal following an Appeal No. A-009-2017 (withdrawn the request for the *in vivo* mammalian comet assay study)[2].
- A Risk Management Optional Analysis (RMOA) is currently under development by Sweden (concern*: Carcinogenic; Mutagenic*). More information is available on the Public Activities Coordination Tool (PACT)[3].

[2] https://194.187.232.199/lv/web/guest/information-on-chemicals/dossier-evaluation-status/-/dislist/details/0b0236e18169a469

[3] https://echa.europa.eu/pact

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 the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION Conclusions	Tick box
Need for follow-up regulatory action at EU level	
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	x

4. FOLLOW-UP AT EU LEVEL

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

Not applicable.

4.1.1. Harmonised Classification and Labelling

Change of existing harmonized classification is not proposed based on the data in the registration dossier.

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

Not applicable.

4.1.3. Restriction

Not applicable.

4.1.4. Other EU-wide regulatory risk management measures

Not applicable.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

Table 2

REASON FOR REMOVED CONCERN The concern could be removed because	Tick box
Clarification of hazard properties/ exposure	x
Actions by the registrants to ensure safety, as reflected in the registration dossiers(e.g. change in supported uses, applied risk management measures, etc.)	

Taking into account the information contained in the registration dossier, the Competent authority of Latvia (eMSCA) was able to conclude on every endpoint of concern and found no potential, inadequately controlled risks.

The exposure concern could be clarified due to the use information provided in the registration dossier. The exposure data did not suggest indications of a risk to consumers.

Hence, it is concluded that the initial concerns can be removed and there is no need for follow-up action at EU level due to this substance evaluation. The Risk Management Optional Analysis (RMOA) currently under development by Sweden is likely addressing other concerns.

5.2. Other actions

Not applicable.

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

Not applicable.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

Vinyl acetate was originally selected for substance evaluation in order to clarify concerns about:

- Suspected reprotoxic;

- Potential endocrine disruptor;

- Suspected sensitiser;

- Consumer use;

- Wide dispersive use;

- High (aggregated) tonnage.

During the evaluation additional concerns were not identified.

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	Outcome/conclusion
Acute toxicity	No further action needed. The current harmonised classification is appropriate.
Skin irritation	Concern not substantiated. No further action.
Eye irritation	Concern not substantiated. No further action.
Sensitisation	Concern not substantiated. No further action.
Repeated dose toxicity	No further action needed. The current harmonised classification is appropriate.
Mutagenicity	Not assessed in detail.
Carcinogenicity	Not assessed in detail.
Reprotoxic properties	Concern not substantiated. No further action.
Endocrine disruptor properties	Concern not substantiated. No further action.
Exposure/Wide dispersive use (consumer use), high (aggregated) tonnage	Concern not substantiated. No further action.

7.2. Procedure

Pursuant to Article 44(2) of the REACH Regulation, vinyl acetate was included in the Community rolling action plan (CoRAP) for evaluation in 2019. The Competent authority of Latvia (eMSCA) was appointed to carry out the evaluation.

The evaluation of vinyl acetate was targeted at human health endpoints and focused on the grounds for concern that were included in the justification document for the inclusion of the substance in the CoRAP. Taking into account all information provided by the Registrants, the eMSCA was able to conclude on every endpoint of concern and found no potential risks which was controlled inadequately.

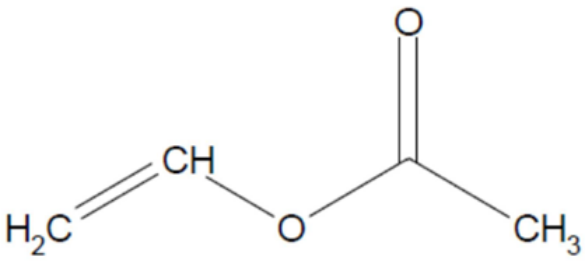
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	Vinyl acetate
EC number:	203-545-4
CAS number:	108-05-4
Index number in Annex VI of the CLP Regulation:	607-023-00-0
Molecular formula:	C4H6O2
Molecular weight range:	86,1 g/mol
Synonyms:	Ethenyl acetate Ethenyl ethanoate Ethenyl ester acetic acid Acetic acid vinyl esther

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

Structural formula:



7.4. Physico-chemical properties

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	Value
Physical state	Liquid (100%) at 20°C and 101.3 kPa
Melting / freezing point	-93.2 °C at 101.3 kPa
Boiling point	72.7 °C at 101.3 kPa
Density	0.93 g/cm³ at 20 °C
Vapour pressure	11.3 kPa at 20 °C
Water solubility	20 g/L at 20 °C
Partition coefficient n-octanol/water (Log Kow)	0.73 at 20 °C
Flash point	-8 °C at 101.3 kPa
Auto flammability	402 °C at 101.3 kPa
Flammability	Highly flammable (100%)
Viscosity	0.42 to 0.43 mPa.s at 20 °C (dynamic)

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- 10,000 t	☒ 10,000-50,000 t
☒ 50,000 – 100,000 t	☒ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☒ > 1000,000 t	☐ Confidential

According to ECHA's dissemination site[4] vinyl acetate is manufactured and/or imported in European Economic area in 1 000 000 - 10 000 000 tonnes per year.

7.5.2. Overview of uses

Vinyl acetate is used by professional workers (widespread uses), in formulation or re-packing, at industrial sites and in manufacturing. Consumers can come into contact to residual levels of vinyl acetate monomer by use of articles.

Described uses of vinyl acetate in the registration(s) represented in Table 7.

Table 7

[4] https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/15530/1

USES	Use(s)
Manufacture	Manufacture of the substance itself
Uses as intermediate	Use as intermediate in industry for manufacturing (polymerisation) of vinyl acetate (co)polymers
Formulation	Polymer production
Uses at industrial sites	Use of monomer in polymerisation processes at industrial site (inclusion or not into/onto article)
Uses by professional workers	PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions; PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions; PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions; PROC 4: Chemical production where opportunity for exposure arises; PROC 5: Mixing or blending in batch processes; PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities; PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities; PROC 15: Use as laboratory reagent; SU 10: Formulation [mixing] of preparations and/or re-packaging (excluding alloys) ; SU 12: Manufacture of plastics products, including compounding and conversion.
Consumer Uses	Negligible consumer exposure to residual levels of vinyl acetate monomer present in adhesives and sealants, cosmetics and personal care products, air care products, fillers, putties, plasters, modelling clay and polymers
Article service life	-

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP Regulation)

According to the harmonised classification and labelling vinyl acetate is classified as specified in Table 8.

Table 8

HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)							
Index No	International Chemical Identification	EC No	CAS No	Classification		Spec. Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement code(s)		
607-023-00-0	vinyl acetate	203-545-4	108-05-4	Flam. Liq. 2 Acute Tox. 4 STOT SE 3 Carc. 2	H225 H332 H335 H351		Note D

7.6.2. Self-classification

- In the registration(s):

Compared to Annex VI of CLP Regulation vinyl acetate has the same classification in the registration(s). Additional classification for Aquatic Chronic 3 (H412: Harmful to aquatic life with long lasting effects) is used by Registrants.

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

Aquatic Chronic 3, H412;
STOT RE 2, H373 (respiratory tract).

7.7. Environmental fate properties

Not evaluated.

7.8. Environmental hazard assessment

Not evaluated.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

A number of studies available in the dossier, showed that vinyl acetate is metabolised rapidly and to a high extent. *In vivo* data where rats exposed by inhalation and oral routes vinyl acetate, showed vinyl acetate to be rapidly and effectively hydrolysed by carboxylesterases leading to the formation of acetic acid and acetaldehyde, which is further converted into acetic acid in the presence of aldehyde dehydrogenases. The toxicokinetics of vinyl acetate have been reviewed in detail under the risk assessment report (EU RAR, 2008). A value of 15% for vinyl acetate uptake during inhalation is recommended as a worst-case scenario for risk assessment.

There are no valid quantitative data on the systemic bioavailability of vinyl acetate and its metabolites following dermal exposure. However, an acute dermal study in rabbits and the fact that carboxylesterase activities are lower in skin compared to nose or oral cavity, it can be assumed that systemic bioavailability of vinyl acetate and/or vinyl acetate-derived metabolites is higher after dermal exposure when compared to oral or inhalative exposure. Therefore, 90 % dermal absorption should be taken forward to the risk characterisation (EU RAR, 2008). The eMSCA can support this conclusion.

7.9.2. Acute toxicity and Corrosion / Irritation

Acute toxicity

In two separate studies using rats, the oral LD_{50} values obtained were 3470 mg/kg (Registration dossier, study report, 1969) and 3500 mg/kg (Registration dossier, study report, 1967).

A dermal LD_{50} value of 7440 mg/kg was determined in a study using rabbits.

Vinyl acetate does not warrant labelling according to CLP Regulation criteria with respect to acute oral and acute dermal toxicity.

Inhalation toxicity testing in rats determined LC_{50} values of 15810 mg/m³/4h (Registration dossier, study report, 1969) and 14084 mg/m³/4h (Registration dossier, study report, 1949).

In one study report, the rats were exposed to vinyl acetate vapour at 2000, 4000 or 8000 ppm (not analytically measured) in glass exposure chambers. All rats exposed to 8000 ppm died during the exposure period. Two male and two female rats died during exposure to 4000 ppm. Clinical signs ranged from redness of extremities and irritation at the lowest dose, to laboured breathing and convulsions at both higher doses. Gross pathology detected haemorrhages in lungs and tracheae in those rats that died at the higher dose levels, whilst there were no remarkable effects at the lowest dose level. Other study reports have shown similar results. In the study, the rats were exposed to vinyl acetate vapours concentration of 4000ppm (14084 mg/m³) for 4 hours and between 2 and 4 out of a total of 6 rats were killed. (Note: The conversion of ppm to mg/m³ is based on MW of 86.09, 25ºC, 1 atmosphere).

Therefore the substance has a harmonized classification -Acute Tox. 4, H332 Harmful if inhaled according to CLP Regulation. Based on the available data, the eMSCA can support this classification.

Human data on the acute toxicity of vinyl acetate are not available.

Corrosion / Irritation

The registrants concluded the substance indicates mild irritation of the skin and eyes of rabbits and therefore do not warrant classification. However, inhalation tests with rats demonstrated severe irritation in the respiratory tract. Thus, vinyl acetate should be classified with STOT - Single exposure Cat 3, H335 May cause respiratory irritation according to CLP Regulation.

Based on available data, the eMSCA can support this classification.

7.9.3. Sensitisation

Two GLP studies are available assessing the skin sensitising potential of vinyl acetate. These include an OECD guideline Local Lymph Node Assay in mice (OECD TG 429) (Registration dossier, study report, 2003) and a non-guideline Buehler assay in guinea pigs (similar to OECD TG 406) (Registration dossier, study report, 1995).

Results from the non-guideline Buehler assay test showed a moderate skin sensitising potential of vinyl acetate (commercial grade).

The Local Lymph Nodes Assay (LLNA) showed no significantly positive stimulation responses at concentrations of 5% - 100%.

Overall, the outcome of both studies may indicate that vinyl acetate is not devoid of a skin sensitising potential. The results of the LLNA do confirm the weak-moderate effects seen in the Buehler test. However, since the positive threshold level was not exceeded in the LLNA, classification and labelling with Skin Sens. Cat. 1, H317 (may cause an allergic skin reaction) according to the CLP Regulation is not warranted.

Based on this information, the substance is not considered to be a sensitising agent in the LLNA assay.The eMSCA can support this conclusion.

No data are available for respiratory sensitisation. There are no observations of respiratory sensitisation during inhalation exposure with the substance in the occupational environment, in spite of the widespread use.

7.9.4. Repeated dose toxicity

No specific organ toxicity was recorded after 90-day repeated oral administration of vinyl acetate with drinking water to rats and mice (Registration dossier, study report, 1980b; 1980c). Groups of rats or mice were exposed to vinyl acetate in drinking water at concentrations of 0, 200, 1000 or 5000 ppm (v/v). The equivalent received doses were 31, 163, 684 mg/kg bw/d for male rats; 36, 193, 810 mg/kg bw/d for female rats; 11, 60, 285 mg/kg/bw/d for male mice; 10, 72, 281 mg/kg bw/d for female mice. The vinyl acetate was 99.9% pure and contained 0.01% acetaldehyde, 0.005% acetic acid, and 0.4% water. There were no deaths during the study and no adverse clinical signs. There was a slight (non-significant) reduction of food consumption and growth retardation in male rats at 5000 ppm that was considered to reflect the 23% reduction in water consumption. There were no treatment-related effects reported for haematology, blood chemistry, organ weights, gross pathology, or histopathology. The NOAEL for both species was 5000 ppm (684 and 810 mg/kg/day for male and female rats, respectively, and 285 and 281 mg/kg/day for male and female mice, respectively).
The value of 281 mg/kg bw/d (female mice) was used by the regsitrants as the NOAEL for systemic effects for risk characterization.

The key study for evaluating the repeated dose toxicity was a combined repeated dose and carcinogenic study via inhalation where rats and mice were exposed to vinyl acetate vapour at concentrations of 0, 50, 200 or 600 ppm (6 hours/day, 5 days/week) over a period of 2 years (Registration dossier, study report, 1988b). The study also included satellite groups for interim evaluation at week 53, interim evaluation at week 83 and a post-recovery evaluation (70 weeks exposure / 15/16 weeks recovery). A reduction in body weight gain was observed for rats and for mice exposed to 600 ppm and for mice exposed to 200 ppm. The NOAEC for systemic toxicity was 200 ppm for rats (704 mg/m³) and 50 ppm for mice (176 mg/m³). For both species, local effects of vinyl acetate exposure were confined to the respiratory system. Morphological non-neoplastic lesions were observed in the nasal cavity of rats and mice exposed to 200 or 600 ppm, in the trachea of mice exposed to 200 or 600 ppm and, in the lungs of the rats and mice exposed to 600 ppm. The NOAEC for local toxicity was 50 ppm (176 mg/m³).

The NOAEC for local and systemic toxicities induced by vinyl acetate inhalation are similar across most of the studies reported. The 2 year combined chronic toxicity and carcinogenicity study on Sprague-Dawley rats and CD-1 mice (Registration dossier, study report, 1988b, Registration dossier, study report, 1994b) was considered to be the most appropriate study from which to derive the NOAEC values.

The $NOAEC_{local}$ is 50 ppm (equivalent to 176 mg/m³) based on respiratory tract effects.
The $NOAEC_{sys}$ is 50 ppm (equivalent to 176 mg/m³) based on bodyweight effects.
Lesions of the respiratory tract epithelia occurred at concentrations above the critical concentration values according to the criteria of CLP Regulation, consequently no classification is warranted for this endpoint. There were no significant toxic effects observed in the 90-day rat and mouse studies which would warrant classification for STOT-RE

according to CLP Regulation guidance (i.e. no relevant adverse effects below 1000 mg/m³).The eMSCA can agree with this conclusion.

7.9.5. Mutagenicity

In the interest of completeness of this evaluation, mutagenicity of vinyl acetate was assessed but not comprehensively. According to the presented *in vivo* and *in vitro* studies, vinyl acetate does not express significant genotoxic activity, which are considered reliable and suitable for classification purposes under CLP Regulation. The eMSCA can agree that the substance is not classified for genetic toxicity.

7.9.6. Carcinogenicity

The potential mechanism(s) of carcinogenicity of vinyl acetate have been extensively evaluated and reported. The carcinogenicity mechanism is assumed to be mediated by the production of acetaldehyde in metabolic reaction. Based on the nonlinear kinetics of intracellular aldehyde dehydrogenase activity there is a marked increase of intracellular acetaldehyde only at high concentrations of vinyl acetate. Overall, the weight of evidence indicates that, for animal carcinogenicity, a threshold mechanism is applicable for vinyl acetate via both inhalation and oral routes of exposure (EU RAR, 2008).

The concentration of 50 ppm (176 mg/m³) is considered as a NOAEC for risk characterisation on carcinogenicity via inhalation. (The conversion of ppm to mg/m³ is based on MW of 86.09, 25 °C, 1 atmosphere.) For the oral route, no NOAEC was estimated (400 ppm for female rats) but this value was proposed as the LOAEC for risk characterisation. However, since oral exposure is not a relevant route of exposure, no oral cancer risk value is to be proposed.

According to CLP Regulation, the classification of vinyl acetate is classified as Carc.2, H351: Suspected of causing cancer. This is in line with the Annex VI of CLP Regulation harmonised classification and the eMSCA can support this conclusion.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

Registrants have identified a number of studies with non-human information. The given information is sufficient to evaluate whether there is an imminent concern for fertility and developmental toxicity, including pre-natal developmental toxicity study in a second species (OECD TG 414) (Registration dossier, 2019).

Effects on fertility

There are sufficient data from a 2-Generation study in rats (Registration dossier, study report, 1995). Groups of 18 to 36 male and female Crl:CD(SD)BR rats were given 0, 200, 1000, or 5000 ppm vinyl acetate via drinking water over two generations.
Vinyl acetate did not produce a consistent effect on reproduction at any of the dose levels tested. Some minor and slight effects on male fertility, not forming a specific pattern, were observed in the high dose group receiving 5000 ppm orally in drinking water, which also induced slight parental toxicity. The changes in fertility parameters included a decrease in fertility of the F1 generation, and a decrease in F1 male mating performance in a cross-mating trial. In addition, the fertility index in a subset of F0 rats mated for the chronic study was lower than that for control rats. The inconsistency of the response across generations and the small magnitude of the changes do not allow a definitive conclusion of compound-related effects to be made. No effects were observed during histopathological examinations of gonads and accessory sex organs in any of the treated groups. More-over, these effects were only observed in doses that induced some parental toxicity (decreased body weight gain and water consumption) and were within the historical control data of the laboratory. No effects were observed on any parameters of female fertility. Based on

these data eMSCA concludes that vinyl acetate shows no specifically toxic effects on fertility.
Another study (Registration dossier, study report, 1988) on testicular genotoxic effects of vinyl acetate after administration of very high doses using an unphysiological route of exposure (i.p.) was considered of no regulatory relevance.

A conservative NOAEL of 1000 ppm in drinking water could be derived for male fertility, and 5000 ppm for female fertility. It can be concluded, these data are sufficient for an adequate hazard and risk assessment. Based on the available data, no classification for fertility (RF) is justified. No further studies are considered necessary. The eMSCA can agree with this conclusion.

Effects on development

There is sufficient data from an oral developmental toxicity study in rats, supported by an inhalation study in the same species, a drinking water two-generation study in rats, as well as a Dose Range Finding (DRF) and a main developmental toxicity study in rabbits (Registration dossier, study report, 2018).

In the developmental toxicity study in rats (Registration dossier, study report, 1980), administration of vinyl acetate in the drinking water during the period of organogenesis (days 6 to 15 of gestation, inclusive) at dose levels up to and including those which produced a degree of drinking water unpalatability did not elicit any developmental effects. Thus, a developmental NOAEL of 5000 ppm v/v in drinking water (477 mg/kg/day) was determined.

In another developmental toxicity study (Registration dossier, study report, 1980) in rats after administration of vinyl acetate by the inhalation route at concentrations up to and including those which produced maternal toxicity did not elicit embryolethality or teratogenicity. At the highest concentration employed (1000 ppm v/v), there was evidence of growth retardation of the foetuses, however this was considered to be a secondary effect of marked maternal growth retardation, and not a direct effect of exposure to vinyl acetate. Thus, the developmental NOAEL of 1000 ppm v/v was determined for inhalation exposure. Unfortunately, no data were available on the degree of absorption of vinyl acetate.

In a two-generation study in rats (Registration dossier, study report, 1995), a minor, slight and inconsistent decrease in pup weight on day 21 post-partum (pp) in the F1 generation, but not in the F2, was the only finding of a developmental effect in the high dose group receiving 5000 ppm orally in drinking water. This is considered secondary to a decreased body weight gain and water consumption of dams during lactation. Consequently, 5000 ppm in drinking water (431 to 765 mg/kg/day, differences are due to the decline in water consumption relative to body weight that occurred over this time period) was found to be the NOAEL for developmental toxicity. Moreover, it can be concluded that vinyl acetate shows no specific toxic effects on development.

In an OECD TG 414 Guideline pre-natal developmental toxicity study in a second species (rabbits), no developmental or maternal toxicity was observed. A NOAEL of 100 mg/kg/day could be determined, which is also supported by the fact that no developmental toxicity (litter size, pup weight, external anomalies) was observed in the DRF study at 200 mg/kg/day, a dose that caused significant maternal toxicity.

Species	Route of administration	Study type	Developmental NOAEL
Rat	Oral via drinking water	Developmental toxicity study	5000 ppm (477 mg/kg)
Rat	Inhalation	Developmental toxicity study	1000 ppm v/v
Rat	Oral via drinking water	Two-generation study	5000 ppm (431 - 765 mg/kg)

Rabbit	Oral gavage	Developmental toxicity study	100 mg/kg

Based on these data, the eMSCA concludes that vinyl acetate shows no indications of inducing developmental toxicity.

7.9.8. Hazard assessment of physico-chemical properties

Not evaluated.

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

For vinyl acetate indicative occupational exposure limit values (IOELV) exist. The IOELV has been established based on the NOAEC of 50 ppm for histological changes in respiratory tissues of rodents and, based on limited observations in humans, the reported threshold for irritancy in humans, considered to be 10 ppm. The adopted STEL is 10 ppm (35.2 mg/m³) and 8 h TWA, 5 ppm (17.6 mg/m³), as concluded by SCOEL in October 2005 (SCOEL/SUM/122) and published in December 2009 (EC, 2009).
15% absorption (uptake) via inhalation, 50% via oral and 90% dermal absorption (both values are used in concurrence with the RAR).
The registrant applied the STEL and TWA values (according to Commission Directive 2009/161/EU) to use as DNEL values.

Table 9

CRITICAL DNELS/DMELS					
Endpoint of concern	Type of effect	Critical study(ies)	Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)	DNEL/ DMEL	Justification/ Remarks
		Workers			
Inhalation	Systemic effects - Long-term		NOAEC 50 ppm	17.6 mg/m³	8h TWA
Inhalation	Systemic effects - Acute			35.2 mg/m³	STEL
Inhalation	Local effects - Long-term			17.6 mg/m³	8h TWA
Inhalation	Local effects - Acute			35.2 mg/m³	STEL
Dermal	Systemic effects - Long-term			0.42 mg/kg bw/day*	

*Dose descriptor The dermal NOAEL can be extrapolated from the IOELV [8 h TWA, 5 ppm (17.6 mg/m³)]. The IOELV is adjusted for differences in uptake between the two routes of exposure (TGD, Appendix R.8-2, Example B.4). It is assumed that uptake of vinyl acetate after inhalation is 15%

while dermal absorption is 90% (as concluded in the RAR (2008)) corrected Dermal NOAEL = IOELV × wRV (human 8 h) × [ABSinhal-human/ABSdermal-human] corrected Dermal NOAEL = 17.6 mg/m³ × 0.144 × [15%/ 90%] corrected Dermal NOAEL = 0.42 mg/kg bw/day. No assessment factor is necessary.

The registrants have not proposed DNELs for the general population exposure because the identified uses for vinyl acetate can not possibly reach threshold levels for the following reasons:

- The sole use identified for vinyl acetate is the use as a monomer in industrial (co-) polymerization processes, and there is no direct consumer use of vinyl acetate monomer.
- Vinyl acetate occurs only as residual monomer in homo- and copolymers, the residual vinyl acetate monomer content in homo- and copolymers (range < 2 - 3000 ppm) depends on the polymer and its field of application. The quantitatively weighted median value of the residual monomer content amounts to 3000 ppm (EU RAR 2008).
- In addition, the initial residual monomer concentration in the polymers decrease rapidly during subsequent processing steps due to off-gassing at industrial facilities as well as due to hydrolysis of residual monomer
- Consumer uses of vinyl acetate (co)polymers with an initial residual vinyl acetate monomer content of significantly less than 3000 ppm may result in consumer exposure at negligible levels.

The eMSCA can support these conclusions. At present there is no need for further information and/or testing or for risk reduction measures beyond those which are already applied.

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

Based on available data eMSCA concludes that existing harmonised classification according to CLP Regulation for vinyl acetate is appropriate.

7.10. Assessment of endocrine disrupting (ED) properties

7.10.1. Endocrine disruption – Environment

Not evaluated.

7.10.2. Endocrine disruption - Human health

A comprehensive review has been carried out by the registrants on evidence regarding the endocrine disruption potential, or lack thereof. The most important conclusions that explain and negate concerns are pointed out in the text below.

Three chronic toxicity/carcinogenicity studies, two of which were GLP-compliant, did not provide any indication for endocrine or adverse effects on endocrine organs caused by vinyl acetate

- upon oral exposure via drinking water in either F344/DuCrj rats or Crj:BDF mice (Registration dossier, study report, 2004); or
- after in utero exposure of the test animals (Sprague Dawley CD rats) that were then treated orally via the drinking water (Registration dossier, study report, 1988a; Registration dossier, study report, 1994a); or
- upon inhalation exposure in either Sprague Dawley CD rats or Crl:CD-1(ICR)BR mice (Registration dossier, study report, 1988b; Registration dossier, study report, 1994b).

A non-conventional two-generation reproduction toxicity study in which Sprague Dawley CD rats were treated orally with vinyl acetate over two generations (Registration dossier, study report, 1995) yielded the following findings that were interpreted as being substance-related (and not, e.g., secondary to the reduced water consumption):

- Although not statistically significant, the F1 fertility index of the 5000-ppm group was lower than that for the control group. The number of litters produced in the high-dose F1 generation was slightly reduced, and this was interpreted by the authors as being caused by reduced fertility.
- When the high-dose group F1 males were cross-mated with the corresponding control F1 females, fewer pups were produced. This was caused by poor mating performance.

In the F1 cross-mating, there were 12 control males available to mate 24 females from the 5000-ppm group and 13 males from the 5000-ppm group available to mate 25 control females. The pregnant females were killed on gestation day 13 and the intrauterine contents examined. The mating index of the female controls/5000-ppm males was 19/25 females mated while the mating index for the 5000-ppm females/control males was 23/24 female mated. The fertility index of the female control/5000-ppm male mating was 19/19 pregnancies while the fertility index for the 5000-ppm female/control male mating was 22/23 pregnancies. In one study report, it is suggested that a possible male-specific effect based on the reduced fertility in the F1a ‘standard’ mating and the reduced mating index in the F1b cross-mating. However, the data does not support this suggestion. First, all of the 13 males in the 5000-ppm group used in the cross-mating experiment produced a pregnancy. This suggests that the reduced fertility index in the F1a mating was probably due to the female animals, not the males used for breeding. The reduced mating index in the F1b female control/male 5000 ppm animals (despite all of the males producing at least one pregnancy) is not easily explained although the method used to mate these animals was extremely unconventional.
Therefore, although it has been indicated that the non-statistically significant finding might be attributed to male fertility, the data do not support this suggestion. The variances observed in this study, and the non-standard, non-guideline approach do not lend enough credible evidence to support that the findings are linked to an endocrine mode of action, nor do they support that there would be sufficient evidence to conclude that endocrine disruption had occurred.

Two prenatal developmental toxicity studies did not yield any maternal or developmental findings that could be attributed as substance-induced ED mediated effects:

- Upon oral exposure via drinking water; and inhalation exposure via whole-body exposure) in Sprague Dawley CD rats (Registration dossier, study report, 1980); findings also published in (Registration dossier, study report 1995);
- Upon oral gavage exposure in New Zealand White rabbits (Registration dossier, study report (2018a, b, c)).

From the available data on vinyl acetate there is no evidence to indicate that there is any alteration of the endocrine system that consequently causes an adverse health effect.

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

Based on the weight of evidence for vinyl acetate, the eMSCA can conclude that vinyl acetate is not an endocrine disruptor.

7.11. PBT and vPvB assessment

Not evaluated.

7.12. Exposure assessment

7.12.1. Human health

7.12.1.1. Worker

The Registrant generated exposure scenarios and made exposure assessment for manufacture, formulation and all the identified end uses using EasyTRA and ECETOC TRA model.
1) Manufacture
2) Distribution of substances
3) Formulation and (re)packing of substances and mixtures
4) Uses in coatings
5) Use in cleaning agents
8) Intermediate
15) Use in laboratories (professional)

The highest exposure value was estimated for workers for inhalation long-term local route for the for polimer production at industrial sites use (PROC 8b: Transfer of substance or preparation). Nevertheless the level of exposure is at an acceptable level.
In the eMSCA's opinion no additional risk management measures are required at the moment.

The eMSCA can conclude that registrant has adequately described the operational conditions and risk management measures for all the scenarios.

7.12.1.2. Consumer

Exposure of vinyl acetate through consumer use was an initial concern, however based on the information in the registration dossier and in the EU RAR 2008, there is only negligible exposure to residual levels of vinyl acetate monomer that can be present in consumer products. Therefore exposure assessment from consumer use is not applicable

7.12.2. Environment

Not evaluated.

7.12.3. Combined exposure assessment

Not evaluated.

7.13. Risk characterisation

Workers

Risk characterisation for workers is based on possible risk from long-term exposure having potential to cause repeated dose toxicity effects. The related reference values - DNELs for inhalation and dermal exposure are applied. It is considered that oral exposure cannot cause any concern in occupational environment.
The exposure scenario with the highest produced vinyl acetate amount per year was selected for risk characterization for repeated dose and long-term acute toxicity. The scenario included following processes: PROC1, PROC2, PROC 8a, PROC 8b, PROC 15.
Risk characterisation for repeated dose toxicity (long-term systemic exposure) for manufacturing of vinyl acetate

	Use in closed process, no likelihood	Use in closed, continuous process with	Transfer of substance or preparation	Transfer of substance or preparation	Use as laboratory reagent

		of exposure PROC1	occasional controlled exposure PROC2	PROC 8a	PROC 8b	PROC 15
Inhalation exposure	The highest exposure concentration estimated (mg/m³)	0.036	6.277	4.484	8.071	5.381
	DNEL (mg/m³)	17.6 mg/m³				
	RCR	< 0.01	0.357	0.255	0.459	0.306
Dermal exposure	The highest exposure concentration estimated (mg/kg bw/day)	0,034	0.027	0.274	0.137	6.8E-3
	DNEL (mg/kg bw/day)	0.42				
	RCR	0.081	0.065	0.653	0.326	0.016
Total exposure	RCR	0.081	0.422	0.908	0.785	0.322

Risk characterisation for repeated dose toxicity (systemic acute exposure)

		Use in closed process, no likelihood of exposure PROC1	Use in closed, continuous process with occasional controlled exposure PROC2	Transfer of substance or preparation PROC 8a	Transfer of substance or preparation PROC 8b	Use as laboratory reagent PROC 15
Inhalation exposure	The highest exposure concentration estimated (mg/m³)	0.143	25.10	17.93	32.28	21.52
	DNEL (mg/m³)	35.2 mg/m³				
	RCR	< 0.01	0.713	0.51	0.917	0.611

The exposure scenario with the highest use of vinyl acetate for polymer production in a year was selected for risk characterization for repeated dose and long-term acute toxicity. The scenario: USE AT INDUSTRIAL SITES included following processes: PROC1, PROC2, PROC 3, PROC 4, PROC 5, PROC 8a, PROC 8b, PROC 15.

Risk characterisation for repeated dose toxicity (long-term systemic exposure) for manufacturing of Vinyl acetate

		Use in closed process, no likelihood of exposure PROC1	Use in closed, continuous process with occasional controlled exposure PROC2	Use in closed batch process (synthesis or formulation) PROC3	Use in batch and other process PROC4	Mixing or blending in batch processes for formulation PROC5	Transfer of substance or preparation PROC 8a	Transfer of substance or preparation PROC 8b	Use as laboratory reagent PROC 15
Inhalation exposure	The highest exposure concentration estimated (mg/m³)	0.036	6.277	1.255	5.022	6.277	4.484	8.071	5.381
	DNEL (mg/m³)	17.6 mg/m³							
	RCR	< 0.01	0.357	0.071	0.285	0.357	0.255	0.459	0.306
Dermal exposure	The highest exposure concentration estimated (mg/kg bw/day)	0,034	0.027	0.014	0.274	0.137	0.274	0.137	6.8E-3
	DNEL (mg/kg bw/day)	0.42							
	RCR	0.081	0.065	0.033	0.653	0.326	0.653	0.326	0.016
Total exposure	RCR	0.081	0.422	0.104	0.938	0.683	0.908	0.785	0.322

Risk characterisation for repeated dose toxicity (systemic acute exposure)

		Use in closed process, no likelihood of exposure PROC1	Use in closed, continuous process with occasional controlled exposure PROC2	Use in closed batch process (synthesis or formulation) PROC3	Use in batch and other process PROC4	Mixing or blending in batch processes for formulation PROC5	Transfer of substance or preparation PROC 8a	Transfer of substance or preparation PROC 8b	Use as laboratory reagent PROC 15
Inhalation exposure	The highest exposure concentration estimated (mg/m³)	0.143	25.10	5.022	20.08	25.10	17.93	32.28	21.52
	DNEL (mg/m³)	35.2 mg/m³							
	RCR	< 0.01	0.713	0.143	0.571	0.713	0.51	0.917	0.611

According to the eMSCA's evaluation, the Risk Characterisation Ratio (RCR = Exposure concentration/DNEL) for workers through inhalation route is below "1" for both industrial usages based on the highest exposure estimate within each use.

As regards the dermal exposure, with assumption that PPE is not used the estimated highest exposure values exceed the RCR value "1". Following, highly protective PPE - nitrile gloves shall be applied to reduce the dermal exposure. In addition, protection against skin sensitisation is ensured as well.

As the above mentioned risks can be managed by appropriate risk mitigation measures, the eMSCA can conclude that there is no overall concern for worker exposure and the risk management indicated in registration dossier by the Registrant are appropriate.

Consumers

Consumer uses of vinyl acetate (co)polymers with an initial residual vinyl acetate monomer content of significantly less than 3000 ppm may result in consumer exposure at negligible levels.

7.14. References

EU RAR 2008

REACH registration dossiers

7.15. Abbreviations

ALD - Approximate Lethal Dose

eMSCA – evaluating Member State Competent Authority

CMR - Carcinogenic, mutagenic or toxic to reproduction

CSR - Chemical Safety Report

DNEL - Derived no-effect level

NOAEC - No observed adverse effect concentration

NOEL - No observed effect level

OECD - Organisation for Economic Co-operation and Development

SVHC – Substance with very high concern