Annex VI Report

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: **Vinyl acetate**

EC Number: **203-545-4**

CAS Number: **108-05-4**

Submitted by: **Germany**

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PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: **Vinyl acetate**

EC Number: **203-545-4**

CAS Number: **108-05-4**

Registration number (s):

Purity: ≥ 99% (w/w)

FOR VINYL ACETATE IN A NOT-STABILIZED FORM

Proposed classification based on Directive 67/548/EEC

For vinyl acetate in a not stabilized form

	Classification	Wording
Hazard Symbols, Indications of danger	Carc. Cat. 3 F Xn Xi	 Highly flammable Harmful Irritant
R-phrases	R11 R19 R20 R37 R40	Highly flammable May form explosive peroxides Harmful by inhalation Irritating to respiratory system Limited evidence of a carcinogenic effect

(Note: No change to the current "no classification" for the environment in Annex VI, Table 3.2 of Regulation (EC) 1272/2008 is proposed.)

Proposed labelling based on Directive 67/548/EEC

	Labelling	Wording
Hazard Symbols, Indications of danger	F Xn	Highly flammable Harmful
R-phrases	R11 R19 R20 R37 R40	Highly flammable May form explosive peroxides Harmful by inhalation Irritating to respiratory system Limited evidence of a carcinogenic effect
S-phrases	(S2) S23 S33 S36/37	Keep out of the reach of children Do not breathe gas/fumes/vapour/spray Take precautionary measures against static discharges. Wear suitable protective clothing and gloves

Proposed classification based on Regulation (EC) No 1272/2008

	Classification	Wording
Hazard classes, Hazard categories	Carc. 2 Flam. Liq. 2 Acute Tox. 4 STOT SE 3	
Hazard statements	H351 H225 H332 H335 EUH019	Suspected of causing cancer Highly flammable liquid and vapour Harmful if inhaled May cause respiratory irritation May form explosive peroxides

Proposed labelling based on Regulation (EC) No 1272/2008

	Labelling	Wording
Pictograms	GHS02 GHS07 GHS08	
Signal Word	Danger	
Hazard statements	H351 H225 H332 H335 EUH019	Suspected of causing cancer Highly flammable liquid and vapour Harmful if inhaled May cause respiratory irritation May form explosive peroxides
Precautionary statements	(P102) P210 P233 P240 P241 P242 P243 P260 P271 P280 P303 + P361 + P353 P304 + P340	(Keep out of reach of children) Keep away from heat/sparks/open flames/hot surfaces. — No smoking. Keep container tightly closed. Ground/bond container and receiving equipment. Use explosion-proof electrical/ ventilating/ lighting/…/equipment. Use only non-sparking tools. Take precautionary measures against static discharge. Do not breathe dust/fume/gas/mist/vapours/ spray Use only outdoors or in a well-ventilated area. Wear protective gloves/protective clothing/eye protection/face protection. IF ON SKIN (or hair): Remove/Take off immediately all contaminated clothing. Rinse skin with water/shower. IF INHALED: Remove victim to fresh air and keep at rest in a position comfortable for breathing.

	P308 + P313	IF exposed or concerned: Get medical advice/ attention
	P363	Wash contaminated clothing before reuse
	P370 + P378	In case of fire: Use … for extinction.
	P403 + P235	Store in a well-ventilated place. Keep cool.
	P405	Store locked up
	P501	Dispose of contents/container to …

(Note: No change to the current "no classification" for the environment in Annex VI, Table 3.1 of Regulation (EC) 1272/2008 is proposed.)

FOR VINYL ACETATE IN A STABILIZED FORM

Proposed classification based on Directive 67/548/EEC

For vinyl acetate in a not stabilized form

	Classification	Wording
Hazard Symbols, Indications of danger	Carc. Cat. 3 F Xn Xi	 Highly flammable Harmful Irritant
R-phrases	R11 R20 R37 R40	Highly flammable Harmful by inhalation Irritating to respiratory system Limited evidence of a carcinogenic effect

(Note: No change to the current "no classification" for the environment in Annex VI, Table 3.2 of Regulation (EC) 1272/2008 is proposed.)

Proposed labelling based on Directive 67/548/EEC

	Labelling	Wording
Hazard Symbols, Indications of danger	F Xn	Highly flammable Harmful
R-phrases	R11 R20 R37 R40	Highly flammable Harmful by inhalation Irritating to respiratory system Limited evidence of a carcinogenic effect
S-phrases	(S2) S23 S33 S36/37	Keep out of the reach of children Do not breathe gas/fumes/vapour/spray Take precautionary measures against static discharges. Wear suitable protective clothing and gloves

Proposed classification based on Regulation (EC) No 1272/2008

	Classification	Wording
Hazard classes, Hazard categories	Carc. 2 Flam. Liq. 2 Acute Tox. 4 STOT SE 3	
Hazard statements	H351 H225 H332 H335	Suspected of causing cancer Highly flammable liquid and vapour Harmful if inhaled May cause respiratory irritation

Proposed labelling based on Regulation (EC) No 1272/2008

	Labelling	Wording
Pictograms	GHS02 GHS07 GHS08	
Signal Word	Danger	
Hazard statements	H351 H225 H332 H335	Suspected of causing cancer Highly flammable liquid and vapour Harmful if inhaled May cause respiratory irritation
Precautionary statements	(P102) P210 P233 P240 P241 P242 P243 P260 P271 P280 P303 + P361 + P353 P304 + P340	(Keep out of reach of children) Keep away from heat/sparks/open flames/hot surfaces. — No smoking. Keep container tightly closed. Ground/bond container and receiving equipment. Use explosion-proof electrical/ ventilating/ lighting/…/equipment. Use only non-sparking tools. Take precautionary measures against static discharge. Do not breathe dust/fume/gas/mist/vapours/ spray Use only outdoors or in a well-ventilated area. Wear protective gloves/protective clothing/eye protection/face protection. IF ON SKIN (or hair): Remove/Take off immediately all contaminated clothing. Rinse skin with water/shower. IF INHALED: Remove victim to fresh air and keep at rest in a position comfortable for breathing.

	P308 + P313	IF exposed or concerned: Get medical advice/ attention
	P363	Wash contaminated clothing before reuse
	P370 + P378	In case of fire: Use … for extinction.
	P403 + P235	Store in a well-ventilated place. Keep cool.
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	P501	Dispose of contents/container to …

(Note: No change to the current "no classification" for the environment in Annex VI, Table 3.1 of Regulation (EC) 1272/2008 is proposed.)

Proposed specific concentration limits (if any):

Proposed notes (if any):

JUSTIFICATION

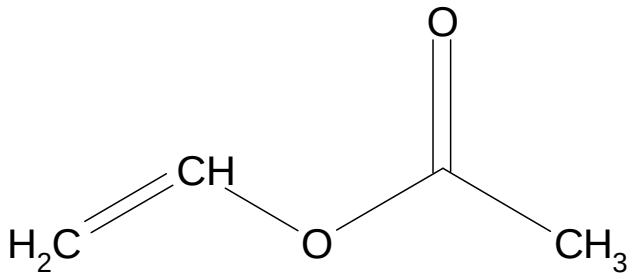
1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Chemical Name: vinyl acetate
EC Name: vinyl acetate
CAS Number: 108-05-4
IUPAC Name: ethenyl acetate

1.2 Composition of the substance

Chemical Name: vinyl acetate
EC Number: 203-545-4
CAS Number:74 108-05-4
IUPAC Name: ethenyl acetate
Molecular Formula: $C_4H_6O_2$
Structural Formula:



Molecular Weight: 86.08 g/mol
Typical concentration (% w/w): Minimum: ≥ 99% (w/w)
Concentration range (% w/w): confidential

1.3 Physico-chemical properties

Table 1.1 Summary of physico- chemical properties

REACH ref Annex, §	Property	IUCLID section	Value	Reference
VII, 7.1	Physical state at 20°C and 101.3 KPa	4.1	liquid	
VII, 7.2	Melting/freezing point	4.2	- 93.2°C	Handbook of Chemistry and Physics 1980 - 1981
VII, 7.3	Boiling point	4.3	+ 72.7°C	Merck Index 1996
VII, 7.4	Relative density	4.4 density	0.932 at 20°C	Merck Index 1996
VII, 7.5	Vapour pressure	4.6	120 hPa at 20°C [1)]	Hoechst AG 1994
VII, 7.6	Surface tension	4.10	24 mN/m at 20°C (pure substance)	Handbook of Chemistry and Physics 1980 - 1981
VII, 7.7	Water solubility	4.8	20 g/l at 20°C [2)]	Merck Index 1996
VII, 7.8	Partition coefficient n-octanol/water (log value)	4.7 partition coefficient	log Pow 0.7 [3)]	Hoechst AG 1992
VII, 7.9	Flash point	4.11	- 8°C (close cup, DIN 51755, NF M07-036)	CHEMSAFE 1994
VII, 7.10	Flammability	4.13	Pyrophoric properties: The classification procedure needs not to be applied because the organic substance is known to be stable into contact with air at room temperature for prolonged periods of time (days). Flammability in contact with water: The classification procedure needs not to be applied because the organic substance does not contain metals or metalloids. EU method A.10 is not applicable because the substance is a liquid. Explosion limits in air: *Lower:* 2.6 vol% *Upper:* 13.4 vol%	BAM II.2 (2010) CHEMSAFE, 2008
VII, 7.11	Explosive properties	4.14	The classification procedure needs not to be applied because there are no chemical groups present in the molecule	BAM II.2 (2010)

			which are associated with explosive properties. Vinyl acetate, unstabilised, is proposed to classify additionally with R19/EUH019. [4] .	
VII, 7.12	Self-ignition temperature		EU method A.16 is not applicable because the substance is a liquid.	BAM II.2 (2010)
VII, 7.13	Oxidising properties	4.15	The classification procedure needs not to be applied because the organic substance contains oxygen, which is chemically bonded only to carbon.	BAM II.2 (2010)
VII, 7.14	Granulometry	4.5	not applicable (no solid)	
XI, 7.15	Stability in organic solvents and identity of relevant degradation products	4.17		
XI, 7.16	Dissociation constant	4.21		
XI, 7.17,	Viscosity	4.22		
	Auto flammability	4.12	385°C (DIN 51794)	CHEMSAFE 1994
	Reactivity towards container material	4.18		
	Thermal stability	4.19	Prolonged or intense exposure to heat may result in polymerization [4)]	
	[enter other property or delete row]	4.23		

1) Vapour pressure:

Vapour pressure values were available from safety data sheets, product information and literature without any details about the used methods. All values correlate well with the boiling point of 72.7°C (Clausius-Clapeyron).

2) Water solubility:

The water solubility is 20 g/l at 20°C according to safety data sheets and product information. No further information about the determination method is available.

3) Partition coefficient:

According to literature data the partition coefficient was determined experimentally (HPLC method: log Pow 0.21, shaking method: log Pow 0.73). The calculation with CLOGP3-Software resulted in a log Pow of 0.7. Due to the agreement of experimentally and calculated values a log Pow of 0.7 was used for the risk assessment.

4) Thermal stability:

VAM is a reactive molecule. Unless inhibited, or if proper handling and storage precautions are not met, VAM can polymerize uncontrollably. VAM is typically shipped with a polymerization inhibitor, hydroquinone or 2-methylhydroquinone. Properly inhibited, VAM is stable under recommended storage conditions. Prolonged or intense exposure to heat, sunlight, ultraviolet light may result in polymerization. Polymerization of VAM is highly exothermic and a rapid release of heat.

2 MANUFACTURE AND USES

2.1 Manufacture

2.2 Identified uses

2.3 Uses advised against

3 CLASSIFICATION AND LABELLING

3.1 Classification in Annex VI of CLP-Regulation

Entry of vinyl acetate in Table 3.2 (The list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Annex VI of Regulation (EC) No 1272/2008 (CLP)

Index-Number: 607-023-00-0

Classification: F; R11 Highly flammable

Entry of vinyl acetate in Table 3.1 of Annex VI of Regulation (EC) No 1272/2008 (CLP)

Index-Number: 607-023-00-0

Classification: Flam. Liq. 2 H225

Vinyl acetate, unstabilised, is proposed to classify additionally with R19/EUH019.

3.2 Self classification(s)

4 ENVIRONMENTAL FATE PROPERTIES

Not evaluated for this dossier.

5 HUMAN HEALTH HAZARD ASSESSMENT

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Following inhalation and oral exposure of rats vinyl acetate is 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 (EU RAR, 2008).

The in vivo uptake of vinyl acetate was measured in the isolated upper respiratory tract of rats (anaesthetised rat, unidirectional flow, and 1 h-exposure). Disappearance of vinyl acetate from the airstream was highest at the lowest exposure concentrations. Greater than 94% extraction was observed at vinyl acetate exposure concentrations of 76 ppm or below. With increasing exposure concentration (76 to 550 ppm), extraction decreased progressively to about 40% and remained at this level up to concentration of approximately 2000 ppm. The impact on blood-flow extraction on vinyl acetate deposition has been calculated by simulating vinyl acetate exposure in the absence of carboxylesterase activity. It could be demonstrated, that blood flow extraction accounts for less than 15% of total vinyl acetate deposition. Hence, 15% inhalative uptake can be taken as a worst case scenario for risk characterisation of systemic effects. However, it should be kept in mind, that vinyl acetate can be degraded in the blood with half lives between < 1 min and 4.1 min.

After oral administration of 297 mg/kg bw ^{14}C vinyl acetate, 63 % of the applied radioactivity was excreted as metabolites in exhaled air, urine and faeces. Based on the fact that vinyl acetate can be metabolized in the upper GI tract epithelium it can be assumed, that a considerable extent of metabolism takes place presystemically which is supported by an oral PBPK model (see below). This model led to the conclusion, that clearance of vinyl acetate and its metabolites into the systemic circulation would be negligible. Hence, 63% absorption would represent an overestimation of systemically available amounts of vinyl acetate. However, the PBPK model developed for oral vinyl acetate exposure did not include systemic components and furthermore, the model was developed in the absence of valid data for carboxylesterases in animal and human tissues. Based on the fact, that carboxylesterases in the GI tract are lower compared to carboxylesterase activities in nasal tissues, 50% absorption can be assumed as a worst case for systemically available amounts of vinyl acetate after oral uptake. However, no clear assumptions can be made for systemically available metabolites of vinyl acetate (acetaldehyde, acetic acid).

There are no valid quantitative data on the systemic bioavailability of vinyl acetate and its metabolites following dermal exposure. However, based on an acute dermal study in rabbits and based on the fact that carboxylesterase activities are lower in skin compared to nose or oral cavity, it can be assumed that systemic bioavailablility 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.

Local metabolism was studied in human and rat nasal respiratory and olfactory tissue with whole turbinates in vitro. The studies indicated species differences of nasal respiratory carboxylesterase activities between rats and humans. The differences varied depending on the mode of data presentation (activity per specimen/activity per epithelial cell volume/activity scaled to whole nose). Therefore, no clear conclusions on the magnitude of species differences of nasal respiratory carboxylesterase activities can be drawn from these investigations. Rat aldehyde dehydrogenase activity in respiratory epithelium was about twice that of humans. Activities of the rat olfactory enzymes (carboxylesterase and aldehyde dehydrogenase) were about equivalent to those of humans. The K_m values for both enzymes are not different between the two species. Aldehyde dehydrogenase activities determined in whole nasal tissue homogenates from mouse, rat, hamster and guinea pig

showed significantly different ratios V_{max}/K_m for the various species indicating the existence of species differences.

Vinyl acetate hydrolysis has been studied in vitro in the oral mucosal tissues from the oral cavity of rats and mice. The hydrolysis activity of the oral tissues is at least 100-fold lower than that of the nasal tissues.

A physiologically based pharmacokinetic model was developed which describes the deposition of vinyl acetate in the nasal cavity of the rat. This model predicts steady state concentrations of the metabolite acetic acid after continuing 6 h-exposure in respiratory tissue which are approximately 13 times greater and in olfactory tissue which are approximately 2 times greater than those of acetaldehyde, the second metabolite. As the concentration of acids is indicative for the concentration of protons the model predicts the greatest reduction in intracellular pH_i for respiratory mucosa. Hence, pH effects should be more pronounced in this tissue as compared to other tissues. This physiologically based toxicokinetic/toxicodynamic model for rat was modified for the olfactory epithelium of the both human and rat nasal cavity. The change in intracellular pH is predicted to be slightly greater for human olfactory epithelium, than that of rats. To provide validation data for this model, controlled human exposures at exposure levels of 1, 5 and 10 ppm to inhaled vinyl acetate were conducted. Air was sampled by a probe inserted into the nasopharyngeal cavity of five volunteers at bidirectional breathing through the nose. Data from ion trap mass spectrometry measurements of labelled vinyl acetate and acetaldehyde were compared with data from the human nasal model simulation. For the vinyl acetate data a good fit was demonstrated ($r = 0.9$). Acetaldehyde data are fitted with a somewhat lower precision. The results show that the human nasal model predicts the experimental observations with regard to vinyl acetate concentrations and the acetaldehyde washout in the airstream of human nasopharyngeal cavity in a concentration range from 1 to 10 ppm. However, uncertainties of the model consist in the enzyme kinetic data used to establish the model. Therefore, data on PK and PD outcome derived from the model should be taken with caution.

A similar PBPK model with a pharmacodynamic submodel for the upper GI tract of mouse, rat and man was developed to estimate oral vinyl acetate uptake, metabolism and the reduction in the intracellular pH. The model was used to estimate steady state concentrations (24 h exposure) of acetic acid, acetaldehyde and intracellular proton concentration in the epithelial cell layer for a range of vinyl acetate exposure from 400 to 10000 ppm in drinking water. Details of model simulations are given for mouse. The intracellular pH reduction from the resting-phase proton concentration is about 0.4 and 0.7 pH units at a vinyl acetate exposure of 400 and 2000 ppm, respectively. Due to missing human data (carboxylesterase activity and tissue thickness) the exact variability in the internal dose-metric in humans cannot be accurately predicted from the PBPK model.

5.2 Acute toxicity

5.2.1 Acute toxicity: oral

Not evaluated for this dossier.

5.2.2 Acute toxicity: inhalation

Species	LC_{50} (mg/l)	Exposure time (h/day)	Observations and remarks
rat	15.8	4h	An acute inhalation range finding study with rats resulted in a LC50 value of 4490 ppm (= 15.8 mg/l/4 hours). Vinyl acetate vapour at metered concentration (not checked analytically) was generated by feeding the liquid at a constant rate down the inside of a spirally corrugated surface of a minimally heated tube, through which metered air was passed. This vapour was delivered in a glass exposure chamber to 6 male and 6 female rats per concentration (8000, 4000 or 2000 ppm). While inhaling 8000 ppm all male and all female rats died during the exposure time (clinical signs: gasping at 10, prostration at 25, convulsions and death at 50 minutes to 1.5 hours). While inhaling 4000 ppm 2/6 male and 2/6 female rats died during the exposure time (clinical signs: laboured breathing at 20 minutes, convulsions at 2.5 hours, death at 3 hours). After inhalation of 2000 ppm no rat died (clinical signs: extremities red and irritated). Gross pathology detected haemorrhages in lungs and tracheae at 8000 ppm, congested lungs and extra fluid in the pleural cavity at 4000 ppm, but no remarkable effects after inhalation of 2000 ppm. (Mellon Institute, 1969)
rat	14.1	4h	In another study vapour concentrations of 96 compounds were examined to evaluate the relative toxicity of a compound independently of its vapour pressure. Response of rats to a single vapour exposure (4-hour vapour exposure) in a 14-day observation period was examined. 4000 ppm vinyl acetate (= 14.1 mg/l) killed 2-4/6 rats within an exposure time of 4 hours. No further data are submitted. (Carpenter et al., 1949)

Species	LC_{50} (mg/l)	Exposure time (h/day)	Observations and remarks
rat	Saturated vapour	1-10 min	In a study on toxicity caused by inhalation of saturated vinyl acetate vapours (temperature used was 20°C). 10/12 rats died within 3 minutes of exposure. Saturated vapours were produced by blowing air through a 5 cm layer of vinyl acetate and inhalation resulted in death of 0/12 rats after 1 minute, 10/12 rats after 3 minutes and 6/6 rats after 10 minutes of exposure. Clinical signs prior to death included severe irritation of mucous membranes, laboured breathing and narcosis. At necropsy, no gross changes were detected. (BASF AG, 1967)

5.2.3 Acute toxicity: dermal

Not evaluated for this dossier.

5.2.4 Acute toxicity: other routes

No data available.

5.2.5 Summary and discussion of acute toxicity

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

In acute toxicity tests by inhalation of vinyl acetate with rats mortality was observed as the main toxic effect. Vinyl acetate fulfils the criteria for classification based on specific 'cut offs' based of LC_{50} values determined in animal testing. Inhalation toxicity testing resulted in LC_{50} values of 15.8 mg/l/4 hours and 14.1 mg/l/4 hours in rats (Mellon Institute, 1969; Carpenter et al., 1949).

Based on the derived LC_{50} values in rats, vinyl acetate is to be classified and labelled as Xn (harmful); R20 (Harmful by inhalation) following the criteria of Council Directive 67/548/EEC (Annex VI: LC_{50}, vapours: 2 – 20 mg/l/4hr). This corresponds to Acute Tox. 4 – H332 according to CLP – Regulation 2008 (Annex I, Part 3, 3.1 Acute toxicity, Category 4, vapours: $10.0 < ATE \leq 20.0$ mg/l/4hr).

5.3 Irritation

5.3.1 Skin

Not evaluated for this dossier.

5.3.2 Eye

Not evaluated for this dossier.

5.3.3 Respiratory tract

Vinyl acetate has proven to cause severe irritation in the respiratory tract of rats. For detailed information see chapter on repeated dose toxicity: inhalation, 5.6.2.

A retrospective study on 21 chemical operators in a production plant with mean age of 45.3 years and mean exposure time of 15.2 years to vinyl acetate vapour with concentrations up to 49.3 ppm (TWA 5.2-8.2 ppm) revealed irritant effects on eyes and respiratory tract that were attributed to high acute exposures (≥21.6 ppm) (Deese and Joyner, 1969) (see Chapter 5.6.4).

5.3.4 Summary and discussion of irritation

Human data on irritation/corrosion caused by vinyl acetate are rare. Data from a retrospective study on 21 chemical operators in a production plant with mean age of 45.3 years and mean exposure time of 15.2 years to vinyl acetate vapour revealed local irritant effects on eyes and respiratory tract that were attributed to high acute exposures (≥21.6 ppm) (Deese and Joyner, 1969).

No specific animal tests for respiratory irritation of vinyl acetate are available. However, inhalation tests with single and repeated exposure of vinyl acetate demonstrated severe irritation in the respiratory tract of the animals.

In acute inhalation tests with rats severe irritation in the respiratory tract of the animals was demonstrated. Rats single exposed to 4000 ppm showed laboured breathing after 20 minutes of exposure, convulsions after 2.5 hours, and death after 3 hours (Mellon Institute, 1969). In another study where rats were single exposed to saturated vinyl acetate vapours (temperature used was 20°C) for 1-10 minutes animals exhibited severe irritation of mucous membranes, laboured breathing and narcosis prior to death (BASF AG, 1967).

Animals repeated exposed to vinyl acetate showed clinical symptoms of respiratory distress with concentration-related frequencies and severity grades. Histopathology of the respiratory tract revealed the cytotoxic type of respiratory irritation. The major toxic effects after prolonged inhalation of vinyl acetate in experimental animals were lesions of the surface epithelium of the upper and lower respiratory tract. Degeneration, regenerative/reparative processes, inflammation, hyperplasia and metaplasia were noted in the nasal mucosa. They were most pronounced in the olfactory epithelium occurring at 200 ppm in rats and mice during and at the end of a 2-year exposure period. Lesions of the respiratory epithelium were seen in mice exposed to 600 ppm during and at the end of 2 years, while rats demonstrated lesions at this site only at a high

concentration of 1000 ppm (4 week study). Characteristic alterations of the larynx and trachea of mice in the 600 ppm groups were hyperplasia and metaplasia along with desquamation and fibrosis in the trachea. Similar changes of the bronchial and bronchiolar airways were reported for rats and mice at this concentration at the end of the 2-year exposure period.

Based on a synopsis of data from acute and repeated dose toxicity studies in experimental animals and of information from a retrospective study on 21 chemical operators where symptoms have been described associated with occupational exposures to vinyl acetate vapour it is proposed to classify vinyl acetate and label for respiratory irritation, i.e. as/with Xi (Irritant); R37 (Irritating to respiratory system) following the criteria of Council Directive 67/548/EEC (Annex VI, 3.2.6.3. Respiratory system irritation) and according to the Annex I rules of CLP – Regulation 2008 (Part 3, 3.8.2.2.1 Respiratory tract irritation) as transient target organ effects, Category 3 of Specific Target Organ Toxicity for single exposure (STOT SE 3; H335, may cause respiratory irritation).

5.4 Corrosivity

Not evaluated for this dossier.

5.5 Sensitisation

Not evaluated for this dossier.

5.6 Repeated dose toxicity

5.6.1 Repeated dose toxicity: oral

Species/strain, group size	Dose (mg/kg bw, mg/kg diet)	Duration of treatment	Observations and remarks (effects of major toxicological significance)
Rat and mouse Rat/Sprague-Dawley or mouse/CD-1 5 sex/group	<u>rat:</u> 0, 50, 200, 1000 or 5000 ppm equivalent to 5, 20, 100, 500 mg/kg bw/d calculated on an assumed water consumption of 10% of body weight) <u>mouse:</u> 0, 50, 150, 1000 or 5000 ppm equivalent to 7.5, 22.5, 150, 750 mg/kg bw/d calculated on an assumed water consumption of 15% of body weight	4 weeks	In oral dose range-finding studies, groups of 5 male and 5 female rats or mice received vinyl acetate in drinking water, rats at concentrations of 0, 50, 200, 1000 or 5000 ppm and mice at concentrations of 0, 50, 150, 1000 or 5000 ppm for 4 weeks (no clinical laboratory investigations, microscopy only of the liver). During the 4th week of treatment the dose level of 50 ppm was increased to 10000 ppm. The results provided the basis for selection of appropriate dose levels for 13-week studies. No deaths occurred during the course of the study in any of the experimental groups. With the exception of one single female mouse at 5000 ppm female mice, which showed tremor and hypothermia, all animals remained healthy throughout the study. Reduction of body weight gain and water consumption was observed in rats, particularly in females, at ≥1000 ppm, in male rats and in male mice at 5000 ppm. Reduced water consumption was also apparent in male mice treated at ≥1000 ppm and in female mice at 5000 ppm, which consumed less food than control females. Lower feed consumption in rats was confined to females treated at 10000 ppm. Data on mean body weight were not reported in the summary document. The only quantitative data given was that reduction in feed consumption was 11% during the first 3 weeks of the study. Absolute and relative liver weights in rats of both sexes and female mice were lower in all treated groups compared to the controls. Microscopy of the liver revealed similar findings in controls and animals treated with 5000 ppm. Thymus weights were reduced in male mice treated with 5000 ppm. There was no evidence of any treatment-related gross abnormalities in organs.

Species/strain, group size	Dose (mg/kg bw, mg/kg diet)	Duration of treatment	Observations and remarks (effects of major toxicological significance)
			(Cont.) The NOAEL for rats was 200 ppm (20 mg/kg bw) based on reduced body weight gain at 1000 ppm; and in mice, the NOAEL was 1000 ppm (150 mg/kg bw) based on tremor and, hypothermia in a single female and reduced thymus weight at 5000 ppm. The toxicological relevance of reduced water consumption and reduced liver weights (in the absence of data on any corresponding morphological or clinical laboratory abnormalities) is equivocal. (Gale, 1979)

Rat and mouse Rat/ Sprague-Dawley CD Mouse/ CD-1, 10 /sex/group	0, 200, 1000 and 5000 ppm <u>male rat:</u> 31, 163, 684 mg/kg bw/d <u>female rat:</u> 36, 193, 810 mg/kg bw/d 0, 200, 1000 and 5000 ppm <u>male mouse:</u> 11, 60, 285 mg/kg bw/d <u>female mice:</u> 10, 72, 281 mg/kg bw/d drinking water	13-weeks study	In oral 13-week studies accepted as valid according to the requirements of the directive 793/93/EEC, groups of 10 male and 10 female rats and mice were administered vinyl acetate in drinking water at concentrations of 0, 200, 1000 and 5000 ppm. The test substance 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 all animals appeared normal. A slight, non-significant degree of growth retardation became prevalent in male rats of the high dose group the mean body weight of these animals was 8% lower than that of controls. The weekly water consumption of male and female rats at 5000 ppm was significantly lower than that of the controls. The overall water consumption was 23% and 25% lower than in control male and female rats. A less marked reduction in water consumption was transiently seen for mid dose male and female rats. No treatment-related effects were seen with respect to haematology, blood chemistry, organ weights, or histopathology. In conclusion, administration of vinyl acetate in the drinking water for 13 weeks at concentrations up to 5000 ppm produced no evidence of organ toxicity in rats and mice representing the NOAEL for both species. (Gale, 1980a,b)
Species/strain, group size	**Dose (mg/kg bw, mg/kg diet)**	**Duration of treatment**	**Observations and remarks (effects of major toxicological significance)**

Rat and mouse		90-day studies	90-day drinking water studies were conducted in rats and mice to determine whether repeated exposure to vinyl acetate correlates with tissue toxicity, measured primarily by cell proliferation in and histopathology of upper digestive tract tissues. Males only were used since they appeared to be slightly more susceptible to neoplasm than females in the Japanese oral cancer study (Umeda et al., 2004). Test solutions were prepared twice weekly; samples of the low and high dose solutions were analysed for concentrations, stability and pH value. Drinking water solutions were daily prepared. Vinyl acetate concentrations taken from solutions in drinking water bottles were stable within 10% of nominal concentrations for at least 4 days. The pH of test solutions decreased with increase of the vinyl acetate concentration and time, e.g., from 5.21 on day 0 to 3.74 by day 4 at 2400 ppm. At this concentration, spontaneous hydrolysis of test compound led to an increase of the acetic acid concentration from 55 ppm at day 0 to 650 ppm by day 4.
<u>Rat/</u> CDF (F344)/ CrlBr 20 m/group	0, 1000, 5000, 10000, or 24000 ppm mean daily intake: 0, 81, 350, 660, 1400 mg/kg bw/d drinking water		Five groups of 20 male rats were administered vinyl acetate in the drinking water for 92 days at concentrations of 0, 1000, 5000, 10000, or 24000 ppm vinyl acetate (99.98%). Animals were weighed and individually observed for body weight development, water consumption and clinical signs of toxicity on a weekly basis. On test days 1, 8, 29, and 92, five rats per group were prepared for evaluation of oral cavity cell proliferation using pulsed 5-bromodeoxyuridine (BrdU) uptake techniques and histopathology of the upper digestive tract tissues (oral cavity, oesophagus, fore stomach, duodenum). Evaluations of the oral cavity for cell proliferation and histopathology were limited to level III (identical to level III of the oral cancer study by Umeda et al., 2004) and level VI from high dose rats and controls. No mortalities or clinical signs of toxicity were attributed to vinyl acetate administration. Rats in the 5000, 10000, and 24000 ppm groups had significantly lower mean body weights (-8.8, -7.4, -6.1%) and mean body weight gains (-13.4, -11, -9.2%) during the study relative to controls. Rats in the 10000 ppm and 24000 ppm groups showed significantly lower mean daily food consumption (-6.0, -7.4%) compared to controls.

Species/strain, group size	Dose (mg/kg bw, mg/kg diet)	Duration of treatment	Observations and remarks (effects of major toxicological significance)

<u>Mouse/</u> B6D2F1/Crl Br (BDF1)	0, 1000, 5000, 10000, or 24000 ppm mean daily intake: 0, 250, 1200, 2300, 5300mg/kg bw/d		(Cont.) Mean daily water consumption was consistently and significantly lower during the study in rats administered water solutions containing 5000 ppm vinyl acetate (-28, -37, -40.3%). No test substance-related gross lesions were observed in the oral mucosa, oesophagus, or fore stomach of rats at any exposure level. Compared to controls, no test-substance related microscopic lesions were observed in the oral mucosa of rats at 24000 ppm. In rats of this group, significant increases in mean cell proliferation occurred in the upper jaw on days 29 and 92 and in the lower jaw on test days 1 and 29. Labelling indices were increased less than 2-fold above the appropriate controls for these groups and were considered to be of equivocal biological significance. A similar study was conducted in mice that received same concentrations of vinyl acetate. Evaluations of the upper and lower jaws for cell proliferation and histopathology were initially limited to level III and V from high-dose and control mice. Subsequently, only the lower jaw from the intermediate groups sacrificed at 92 days was evaluated to determine a NOEL for cell proliferation. All mice survived to their scheduled termination without any clinical sign of treatment-related toxicity. No vinyl acetate induced effect on body weight was observed. At various intervals during the study, mice from all test groups had significantly lower mean food consumption compared to controls. However for the period day 0-92 no significant difference was observed. The mean daily water consumption was significantly lower in mice from all test groups at various intervals and for the period day 0-92 (-23, -30.5, -31.4, -35%). No test substance-related gross lesions were observed in the oral mucosa, oesophagus, or fore stomach of mice at any exposure level. Compared to controls, no test-substance related microscopic lesions were observed in the oral mucosa of mice at 24000 ppm. Significant and dose-related increases in mean cell proliferation occurred in the lower jaw of mice from the 10000 ppm and 24000 ppm groups but only at 92 days.

Species/strain, group size	Dose (mg/kg bw, mg/kg diet)	Duration of treatment	Observations and remarks (effects of major toxicological significance)
			(Cont.) The increases were approximately 2.4 to 3.4-fold above the control groups mean for the 10000 ppm and 24000 ppm groups, respectively. Based on the magnitude of the increases and the dose-related nature of the response, these increases were considered to be compound-related. (DuPont, 2000; Valentine et al., 2002)
Rat/ F344/DuCrj Mouse (Crj:BDF1) No further data on animals/sex/ group, etc.)	0, 600, 1500, 3800, 10000, 24000 ppm	13 weeks	No treatment-related histopathological findings were reported in a short communication on dose-range finding studies in rats and mice at concentrations of 0, 600, 1500, 3800, 10000 or 24000 ppm vinyl acetate in the drinking water after 13 weeks treatment. Water consumption was affected at 24000 ppm (calculated on an assumed water consumption of 10% in rats, resp. 15% in mice to be equivalent to 2400 mg/kg bw/d for rats, resp. 3600 mg/kg for mice). Main study reported in 5.8.1 Carcinogenicity: oral. (Umeda et al., 2004)

5.6.2 Repeated dose toxicity: inhalation

Species, Strain, group size	conc	Exposure time	Duration of treatment	Observations and remarks (effects of major toxicological significance)
Rat Alderly Park (SPF) 4/sex/ group	0, 100, 250, 630 or 2000 ppm Calculated as 0, 360, 890, 2200, 7100 mg/m³	6 h/day	15 days in about 3 weeks	In a less well documented study (no details on parameters of laboratory investigations, no data on food consumption, no list of organs for microscopic examination or results) groups of 4 male and 4 female rats were whole body exposed to vinyl acetate (no data on purity and details on exposure chamber) at 0, 100, 250, 630 or 2000 ppm 6 hours/day, 15 days in about 3 weeks. Animals exposed to 2000 ppm showed signs of eye and nose irritation, respiratory difficulties, and reduced body weight gain (no quantitative data). At microscopy increased numbers of macrophages in the lungs were observed. Females of the 630 ppm and 250 ppm groups also had lower body weight gain. Autopsy revealed normal organs up to 630 ppm. At 100 ppm and 250 ppm blood and urine tests were reported to be normal. There were no data on these tests for other dose groups. Based on this short note, the NOAEC for systemic effects was 100 ppm (360 mg/m³) in female rats and at 250 ppm (890 mg/m³) in male rats. The NOAEC for local effects on the respiratory tract was 630 ppm (2200 mg/m³). (Gage, 1970)

Species, Strain, group size	conc	Exposure time	Duration of treatment	Observations and remarks (effects of major toxicological significance)
Rat Sprague-Dawley CD 5/sex/ group	0, 50/1500, 150, 500 or 1000 ppm calculated: 0, 180, 540, 1800, 3600 mg/m³	6h/day	5 d /week, 4-weeks	In a 4-week range-finding study groups of 5 male and 5 female rats were exposed to 0, 50/1500, 150, 500 or 1000 ppm of vinyl acetate vapour, 6 hours/day, 5 days/week (no data on the purity of the test substance, acetaldehyde concentration in the exposure chamber 8 ppm). The concentration of 50 ppm was increased to 1500 ppm (5360 mg/m³) on exposure day 10 as marked clinical effects had not been observed at 1000 ppm. The studies did not incorporate examinations on haematology, clinical biochemistry or urinalysis. Multiple samples from tissues/organs were preserved, but were not processed for histopathology. The reports available did not contain figures and tables. Rats exposed to ≥500 ppm intermittently showed hunched posture and respiratory distress with dose-related frequencies and severity grades. A dose-related (non significant) decrease in body weight gain was noted in females of all treatment groups and in males of 50/1500 ppm and 1000 ppm groups. No treatment-related macroscopic abnormalities were observed at necropsy. The absolute and relative weights of spleen were decreased in males exposed to ≥1000 ppm. Concentrations of ≥500 ppm in rats produced clinical signs of respiratory tract irritation. As growth retardation was not significant, the NOAEC for systemic effects was 1500 ppm in rats (5360 mg/m³). The NOAEC for local effects on the respiratory tract was 150 ppm in rats (540 mg/m³). (Owen, 1979b)

Species, Strain, group size	conc	Exposure time	Duration of treatment	Observations and remarks (effects of major toxicological significance)
Mouse CD-1 5/sex/ group	0, 50/1500, 150, 500 or 1000 ppm calculated as: 0, 180, 540, 1800 and 3600 mg/m³)	6h/day	5 d/week, 4-weeks	Mice exposed to ≥150 ppm intermittently showed hunched posture and respiratory distress with dose-related frequencies and severity grades. Mean body weight gain was decreased in all treated mice, however it gained significance only in males and females of the 1000 ppm group and in females of the 50/1500 ppm group. No treatment-related macroscopic abnormalities were observed at necropsy, the absolute and relative weights of spleen were decreased in males exposed to 1500 ppm. Concentrations ≥150 ppm produced clinical signs of respiratory tract irritation. As growth retardation was not significant, the NOAEC for systemic effects was 1500 ppm in mice (5360 mg/m³). However with respect to the limited test parameters, the confidence of statements on systemic toxic effects was low. The NOAEC for local effects on the respiratory tract was 50 ppm (180 mg/m³) in mice of both sexes. (Owen, 1979a)
Rat Sprague-Dawley (Crl:CD BR)) 5 m/group	0, 50, 200, 600, 1000 ppm	6 h/day	5 days /week 1, 5 or 20 days	The effects of vinyl acetate exposure on nasal epithelial cell proliferation were evaluated in male rats exposed for 1, 5, or 20 days (6 h/d, 5 days per week) to 0, 50, 200, 600, or 1000 ppm. The test material was 99.9% pure. Impurities consisted of acetaldehyde (100 ppm), acetic acid (50 ppm), hydroquinone stabiliser (3-7 ppm), ethylacetate (300 ppm), and methylacetate (200 ppm). Respiratory tract tissues were examined for gross alterations. Cell proliferation was assessed by histopathological evaluation of five cross sections of the nose and by immuno-cytochemistry (level of BrdU incorporation following BrdU injection 18 hours after the last exposure).

Species, Strain, group size	conc	Exposure time	Duration of treatment	Observations and remarks (effects of major toxicological significance)
				(Cont.) Data on feed consumption were not reported. There were no changes in body weight except to a reduced mean body weight in the 1000 ppm group from day 3 (maximum reduction on day 5: -14%) through day 26 (-11%). Following a single exposure, rats of the 600 ppm and 1000 ppm groups showed concentration-related minimal to moderate degeneration, necrosis and exfoliation of the olfactory epithelium and only at 1000 ppm minimal degeneration and necrosis in the respiratory epithelium. Following 5 or 20 exposures, additional lesions consisted of mild to severe regenerative hyperplasia with attenuation and/or disorganisation of the olfactory mucosa, occasionally squamous metaplasia and only after 20 exposures minimal to severe degeneration and atrophy of olfactory nerve bundles. Respiratory epithelium showed minimal regenerative hyperplasia and only after 20 exposures minimal squamous metaplasia. A significant concentration-related increase in cell labelling was observed in the basal cells of the respiratory and olfactory epithelium following a single 6-hour exposure to 600 ppm and 1000 ppm. No significant difference in labelling indexes of the respiratory and olfactory epithelium was observed after 5 days of exposure. Following 20 days of exposure, the response in the respiratory epithelium remained near control levels while that in the olfactory epithelium was significantly higher in the 600 ppm and 1000 ppm groups than control levels. Again basal cells were labelled, but additional labelling of cells was seen in the adluminal regions of regenerating epithelium. The NOAEC for nasal effects was 200 ppm in this study (710 mg/m³). (Bogdanffy et al., 1997)

Species, Strain, group size	conc	Exposure time	Duration of treatment	Observations and remarks (effects of major toxicological significance)
Rat Sprague-Dawley CD 10/sex/group	0, 50, 200 or 1000 ppm (calculated 0, 180, 710, 3600 mg/m³)	6h/day	5 d/wk, 90 days	In a 90-day inhalation study groups of 10 male and 10 female rats were whole body exposed to vinyl acetate vapours (purity of test substance 99.9%) at concentrations of 0, 50, 200 or 1000 ppm, 6 h/day, 5 days/week. Histopathological sections from several tissues from all animals of the high concentration and the control groups were examined; the nasal turbinates (without any information about the number of sections) were included. The reports did not contain histopathology summary tables. The findings of the nasal mucosa were not separately reported for the respiratory and olfactory epithelia. No feed consumption data are available. Exposure of rats to 1000 ppm resulted in significantly decreased body weight gain (final body weight: -19% in both sexes), clinical effects (intermittent incidence of respiratory distress, hunched postures and ruffled fur), increased lung-to-body weight ratio (assumed as due to lung congestion), and histomorphological changes in the respiratory tract (mild histiocytic alveolitis). The study authors assumed that increased relative lung weights were related to congestion. This association seems not to be plausible because lung congestion was reported for one incidental death in the control group. The quality of the rat study was considered to be restricted, because most control and high dose rats suffer from parasitic infections indicated by eosinophilic gastritis and colon nematodiasis. Many rats from both groups had peribronchial/perivascular lymphoid hyperplasia, alveolar histiocytosis/ histiocytic pneumonia, chronic tracheitis and laryngitis, and lympadenitis. Except a higher incidence of alveolar histiocytosis in high dose rats (19/20 vs. 12/20 controls) no treatment-related toxic effect was seen in the organs examined.

Species, Strain, group size	conc	Exposure time	Duration of treatment	Observations and remarks (effects of major toxicological significance)
				(Cont.) The olfactory regions of nasal sections of 4 males and 3 females (of this study) exposed to 1000 ppm were reviewed by Hardisty et al. (1999). The most severe lesions were seen in the dorsal medial meatus of the anterior nasal passages (level II), lesions extended posteriorly to the dorsal medial meatus of levels III and IV and the dorsal scroll of the third ethmoturbinates. Lesions were characterised by postdegenerative atrophy of the olfactory epithelium and focal erosion, with associated infiltration of neutrophils and eosinophils. Some loss of Bowman's glands and of nerve bundles in the lamina propria was observed in the most severely affected areas. There was only a minimal evidence of regeneration of the affected epithelium. On the limited data of this study, a NOAEC for systemic effects was 200 ppm (710 mg/m³) for the rat (due to growth retardation at 1000 ppm). The NOAEC for local effects on the respiratory tract was 200 ppm (710 mg/m³) for rats due to respiratory distress and higher incidences of alveolar histiocytosis. (Owen, 1980b; Hardisty et al., 1999)

Species, Strain, group size	conc	Exposure time	Duration of treatment	Observations and remarks (effects of major toxicological significance)
Mouse (CD-1) 10/sex/group	0, 50, 200, 1000 ppm calculated as: 0, 180, 710 or 3600 mg/m³)	6h/day	5 d/wk, 90 days	Groups of 10 male and 10 female CD-1 mice were whole body exposed to vinyl acetate vapours (purity of test substance 99.9%) at concentrations of 0, 50, 200 or 1000 ppm, 6 hours/day, 5 days/week. Histopathological sections from several tissues from all animals of the high concentration and the control groups were examined; the nasal turbinates (without any information about the number of sections) were included. Histopathology examinations were extended to 2 levels of nasal turbinates, 3 lobes of the lungs and 3 levels of the trachea for all animals of the low and intermediate groups. The reports did not contain histopathology summary tables and tabulated data were totally absent. The findings of the nasal mucosa were not separately reported for the respiratory and olfactory epithelia. No feed consumption data are available. Exposure to 200 ppm produced transient signs of respiratory distress and hunched posture through the first 9 days of exposure. High dose males and females exhibited ruffled fur, hunched posture and respiratory distress. Six high dose females, three high dose males and two male controls died during the course of the study, all except one death were associated to the routine blood sampling. There was a significant reduction of body weight gain in the groups of high dose males (-18%) and females (-17%). Microscopic changes including inflammatory, transudation and eosinophilic homogenous material in the nasal passages, hyperplasia of goblet cells hyperplastic and metaplastic changes of the nasal turbinates, (suspected) areas of epithelial metaplasia or hyperplasia of the trachea with loss of ciliated epithelium and epithelial atrophy, multifocal bronchiolitis, bronchiectasis, bronchial epithelial metaplasia and hyperplasia, and occasional bronchiolar and bronchial exudation were seen in high dose male and female mice.

Species, Strain, group size	conc	Exposure time	Duration of treatment	Observations and remarks (effects of major toxicological significance)
				(Cont.) Mild to slight inflammation of the nasal turbinates were observed in one low dose female and three intermediate dose females, a very mild accumulation of eosinophilic homogenous material was observed in the nasal passages of two low dose female mice, and two mid dose females exhibited mild bronchiolitis. The study authors considered this mild change to be similar to that seen in the control animals, although no findings were reported for control mice. Although similar lesions may occasionally be observed in historical controls, these findings were consistent to those of the high dose mice. Therefore this interpretation is considered to be equivocal. Based on the data of this study, a NOAEC for systemic effects was 50 ppm (180 mg/m³) for the mouse (due to hunched posture at 200 ppm and above). However, it is uncertain whether hunched posture could be interpreted as a non-specific toxic effect, more likely it seems to be associated with the respiratory symptoms. The NOAEC for local effects on the respiratory tract was 50 ppm (180 mg/m³) for mice due to respiratory distress at 200 ppm and under the assumption that the morphologic lesions of the respiratory tract of mid and low dose were incidental. (Owen, 1980a)

Species, Strain, group size	conc	Exposure time	Duration of treatment	Observations and remarks (effects of major toxicological significance)
Rat and mouse <u>Rat</u> Sprague-Dawley (Crl:CD (SD)BR <u>Mouse</u> CD-1 (Crl:CD-1(ICR)BR 60/sex and dose 3 satellite groups of 30 of each species and sex for interim evaluation	0, 50, 200, 600 ppm equivalent to: 0, 178.5, 714, 2142 mg/m³	6h/day	5 days/ week, 2 years	In a combined chronic toxicity and carcinogenicity study male and female Sprague-Dawley rats and CD-1 mice including 60 animals per sex per dose and three satellite groups of 10 of each species and sex for interim evaluation at week 53 and week 83 and recovery studies (70 weeks of exposure followed by 15/16 weeks of recovery) were exposed by inhalation to vinyl acetate vapour in concentrations of 0, 50, 200, and 600 ppm over a period of 2 years (6 hours/day, 5 days/week). The test material contained impurities of acetaldehyde (≤65 ppm), acetic acid (≤10 ppm), water (≤472 ppm) and hydroquinone (≤1 ppm). Examinations on haematology, clinical biochemistry, urinalysis and gross and microscopic abnormalities were performed on satellite groups at week 51 and 81 and on the end of the main study. At the end of the study, a significant reduction in weight gain (no quantitative data available) was observed among rats and mice in the 600 ppm groups (final body weights -10% in males to -15% in females). Also, the overall body weight gain of 200 ppm mice was significantly lower than that of the control groups (no quantitative data reported). Increases in weight gain were noted in the recovery groups of high dose male rats, the high dose male mice and females of all doses. Exposed animals of both species at all concentrations showed rough haircoat and hunched posture. There were effects on blood glucose (reduced in high dose female rats) and urinary parameters (decreased urine volume and pH values and increased specific gravity in high dose rats) which were attributed to (non-measured) reduced food and water consumption. The survival rates of 600 ppm female rats were higher than that of controls, (64% vs. 36%), but overall there was no treatment-related increase in mortality in both species. In both species exposure-related effects were confined to the respiratory system.

Species, Strain, group size	conc	Exposure time	Duration of treatment	Observations and remarks (effects of major toxicological significance)

				(Cont.) Mean lung weight was increased in high dose rats (relative weights) and mice (absolute and relative weights). Lung weight was also affected in low and intermediate dose rats and intermediate dose mice, however the effect was inconsistently found after several intervals of treatment. In both species of each sex, vinyl acetate induced morphological nonneoplastic lesions in the nasal cavity of the 200 ppm and 600 ppm groups and in the trachea (mice only) and in the lungs of the 600 ppm groups. In addition, some high dose female mice showed hyperplastic lesions in the larynx (no data on exact number of affected animals), a focus of squamous epithelial hyperplasia with dysplastic changes was noted in a single female. In rats, nasal lesions were restricted to the olfactory mucosa consisting of atrophy and basal cell hyperplasia, in severe cases lesions were accompanied with replacement of respiratory epithelium, non-keratinising squamous metaplasia, thickened and oedematous submucosa, loss of nerve bundles and Bowman's glands or with hyperplasia of glandular structures. In the 200 ppm groups, lesions were restricted or most pronounced in the anterior part of the dorsal meatus, which is normally covered by the olfactory epithelium. At 600 ppm, the lesions extended to the posterior parts of the olfactory epithelium. In this area, a layer of stratified non-differentiated epithelium containing small foamy structures resembling nerve bundles and groups of epithelial cells resembling acinar cells of the Bowman's glands was evident in many rats of the 200 ppm groups and a few rats of the 600 ppm groups. They were often accompanied by keratinising squamous epithelium and epithelial nest-like infolds. The study authors considered this being a complete regeneration. - Mice of the 200 ppm and 600 ppm groups showed similar lesions, however differed in that the olfactory epithelium was replaced by respiratory-like epithelium and the sustentacular cells were more frequently hypertrophic and showed loss of sensory cells.

Species, Strain, group size	conc	Exposure time	Duration of treatment	Observations and remarks (effects of major toxicological significance)
				(Cont.) In high dose mice only, non-keratinising squamous metaplasia of the respiratory epithelium, nasal inflammatory infiltrate and exudate were observed. Also, the trachea was affected showing hyperplastic epithelium, occasionally with epithelial flattening, exfoliation, metaplasia and fibroepithelial projections. In the lung of both species exposed to 600 ppm bronchial/bronchiolar epithelium was flattened or exfoliated, and showed intraluminal fibroepithelial projections and alveolar (or interstitial) accumulation of macrophages with pigments and foamy or eosinophilic appearance. Treatment-related nasal and pulmonary lesions in rats and mice were similar in the interim and recovery groups to those seen in the main study and occurred at about the same incidence and the same or lower degree as in the main study. In the lungs bronchial exfoliation was not observed in any of the interim or recovery group rats. Cessation of treatment for 16 weeks showed no recovery from olfactory atrophy in rats and mice, although high dose mice did show a tendency to recover from the inflammatory changes and epithelial hyperplasia. No hyperplasia of the tracheal epithelium was seen in the recovery group of mice. In summary, the chronic inhalation of ≥200 ppm vinyl acetate vapour induced cytotoxic effects on the epithelia of the upper and lower respiratory tract of rats and mice accompanied by nasal inflammation in mice. The NOAEC for local effects on the respiratory tract was 50 ppm for both species (180 mg/m³). Based on the reduction of body weight gain, the NOAEC for systemic toxicity was 200 ppm for rats (710 mg/m³) and 50 ppm for mice (180 mg/m³). (Owen, 1988; Bogdanffy et al., 1994b)

5.6.3 Repeated dose toxicity: dermal

No data available

5.6.4 Other relevant information

Human data

Data from a retrospective study on 21 chemical operators in a production plant with mean age of 45.3 years and mean exposure time of 15.2 years to vinyl acetate vapour revealed local irritant reactions attributed to occasionally high acute exposures. During two sampling periods spaced by one month within a total sampling period of 18 months a total of 40 separate determinations on vinyl acetate concentrations were made in three production units. 14 control operators from other production sites of the plant were examined. Concentration values ranged from 0 to 49.3 ppm with a mean of 8.6 ppm (TWA 5.2-8.2 ppm). No striking differences in health analysis were noted. Retrospective analysis of medical records during the past five years indicated that vinyl acetate operators had longer time of absence due to respiratory conditions. Self recording of clinical signs of irritation during the sampling period revealed that levels of 21.6 ppm produced eye irritation. The authors concluded that no significant eye/upper respiratory tract irritation was noted at concentration below 10 ppm, however single subjects noted eye irritation or hoarseness already at concentrations of 4.2 to 6.8 ppm). Three subjects exposed to 21.6 ppm experienced cough and/or hoarseness and produced intolerable eye irritation (Deese and Joyner, 1969). Bias by co exposure to other compounds was not excluded in this report. Vinyl acetate concentrations in 'non-exposed' control rooms ranged from nil to 9.9 ppm with a range of mean values from 0.2 to 6.6 ppm.

5.6.5 Summary and discussion of repeated dose toxicity:

Oral

No specific organ toxicity was recorded after repeated oral administration with drinking water of vinyl acetate to rats and mice. A subchronic 13-week study revealed a slight (nonsignificant) reduction of food consumption and growth retardation in male rats at 5000 ppm (calculated to correspond to 684 mg/kg bw/d) (Gale, 1980a,b) that was supposed to be related to the 23% reduction in water consumption. Thus, the NOAEL for both species was estimated to be 5000 ppm.

Elevated rates of cell proliferation in the mucosa of the oral cavity was observed in mice exposed for 92 days to vinyl acetate concentrations of 10000 ppm (5300 mg/kg bw/d) and rats exposed to 24000 ppm (1400 mg/kg bw/d) (DuPont, 2000; Valentine et al., 2002). The NOAEL for the mitogenic response was 5000 ppm (1200 mg/kg bw/d) in the mouse study and 10000 ppm (6600 mg/kg bw/d) for the rat study.

The outcome of all oral repeated dose toxicity studies on vinyl acetate gives no indications that vinyl acetate induced toxic effects within the critical dose range for Xn, R48/22 or STOT Rep.2, respectively. Therefore, no classification/labeling is proposed for repeated dose toxicity via the oral route.

Inhalation

No premature deaths were confined to prolonged vinyl acetate treatment up to the highest tested concentrations of 2000 ppm in the rat and of 1000 ppm in mice. Rough hair coat and hunched posture was observed on rats and mice exposed to vapour concentrations of 50 ppm and higher for 2 years (Bogdanffy et al., 1994b; Owen, 1988). Prolonged inhalation exposure of rodents to higher concentrations of vinyl acetate vapour induced clinical signs of growth retardation, eye and nose irritation, hunched posture, rough fur, respiratory distress and reduced urine volume. A reduction of body weight gain observed in mice ≥200 ppm and in rats ≥600 ppm after exposure over 2 years may be associated to non-specific toxicity of vinyl acetate. It was interpreted to be attributed to lower food and water consumption, but the 2-year study did not contain any data on the consumption of water/food and the food efficiency. Reduced urine volume observed in rats at 600 ppm of the 2-year study (Bogdanffy et al., 1994b) was not accompanied by other morphological or functional abnormalities. No clear toxic effect could be identified in parenchyma outside the respiratory tract.

Main effects of vinyl acetate were the local toxic effects on the upper and lower respiratory tract. Rats and mice exposed repeatedly demonstrated degeneration, partly accompanied by regenerative/reparative processes and occasionally inflammation, hyper- and metaplasia of the surface lining epithelia of the nose. Lesions of the nasal cavity were found in the epithelium of the olfactory and respiratory regions being more pronounced in the olfactory epithelium. Rats exposed to concentrations of 200 ppm or higher over a period of 2 years (Bodganffy et al., 1994b; Owen, 1988) developed degenerative lesions of the olfactory mucosa. In the respiratory epithelium of the nasal turbinates, lesions were evident in this species at 1000 ppm after 4 weeks of vinyl acetate inhalation (Bogdanffy et al., 1997). At the end of the study, cell proliferative rates were significantly increased in the olfactory epithelium at ≥600 ppm, but no response was seen in the respiratory epithelium up to 1000 ppm. Mice exposed at 200 ppm for a period of 2 years showed degenerative lesions of the olfactory mucosa. Squamous metaplasia was noted in the respiratory mucosa at a concentration of 600 ppm accompanied by prominent inflammatory infiltration (Bogdanffy et al., 1994b). Hyperplasic and metaplastic alterations of the larynx and trachea together with epithelial desquamation and fibrotic reactions of the tracheal epithelium were exclusively found in mice at a concentration of 600 ppm within 2 years (Bogdanffy et al., 1994b; Owen, 1988). Similar changes were found in the bronchial and bronchiolar airways of rats and of mice at this concentration and exposure duration. In addition histiocytic cell accumulation in the alveoli and interstitium of the lung was observed being possibly related to increased lung weights.

As lesions of the respiratory tract epithelia occurred at concentrations above the critical concentration values for Xn, R48/20 (≤0.25 mg/l, 6h/d) according to the Annex VI criteria given in Directive 67/548/EEC and STOT Rep.2 (≤0.2 mg/l, 6h/d) according to CLP Regulation (2008), Annex I, Part 3.9, there is no need for classification and labelling with respect to repeated dose toxicity.

Dermal

No data available.

5.7 Mutagenicity

5.7.1 In vitro data

Table 5.1 In vitro tests: bacterial genotoxicity

	Concentration range					
Test system	With S-9 mix	Without S-9 mix	Result	Toxicity	Remarks	Reference
Salm. typh. TA98, TA100, TA1535, TA1537	yes	yes	neg	no data	rat liver S-9 mix; tested doses not clearly specified	McCann et al., 1975
Salm. typh. TA100, TA1530	0.003%, gas phase		neg	total toxicity at 0.02% and higher doses	mouse liver S-9 mix with and without cofactors	Bartsch et al., 1979
Salm. typh. TA102	up to 5000 µg/plate	up to 5000 µg/plate	neg			Jung et al., 1992
Salm. typh. TA98, TA100, TA1535, TA1537	no data	no data	neg	no data	screening paper without details	Florin et al., 1980
Salm. typh. TA98, TA100, TA1535, TA1537, TAQ1538	up to 1000 ug/plate	up to 1000 ug/plate	neg	no data	screening paper without details; use of rat and hamster liver S-9 mix	Lijinski & Andrews, 1980
Salm. typh. TA97, TA87, TA100	100 to 500 ug/ml	100 to 500 ug/ml	neg	no data	screening paper without details	Brams et al., 1987
Salm. typh. TA98, TA100, TA1535, TA1537 E. coli WP2 uvr/pKM 101	1.22-5000 µg/plate	1.22-5000 µg/plate	neg	no data	only test result tables, original data in Japanese	JETOC, 2004
E. coli PQ37	130 to 8600 ug/ml	130 to 8600 ug/ml	neg	no data	screening paper without details	Brams et al., 1987

Table 5.2 In vitro tests: mouse lymphoma assay, chromosomal mutations and micronuclei

	Concentration range					
Test system	With S-9 mix	Without S-9 mix	Result	Toxicity	Remarks	Reference
chrom. ab. in human lymphocytes	not done	0.1 to 1 mmol/l	pos	no data	48-h treatment; pos at 0.2, 0.5 and 1 mmol/l (isol. lymp.), or 0.5 and 1 mmol/m (whole blood); extremely steep dose-effect-relationship; max. eff. ca. 90% aberrant cells	Norppa et al., 1985
chrom. ab. in human lymphocytes	not done	0.125 to 2.0 mmol/l	pos	clear inhibition of mitotic activity at 0.5 mmol/l and higher	24-h treatment; pos at 0.25 to 2.0 mmol/l (isol. lymph. and whole blood); max. eff. >40% aberrant cells	Jantunen et al., 1986
chrom. ab. in human lymphocytes	not done	0.5 mmol/l	pos	no data	vinyl acetate was used as positive control	Mustonen et al., 1986
micronuclei in human lymphocytes	not done	0.125 to 2.0 mmol/l	pos	no data	48-h treatment; pos for doses of 0.5 and 1.0 mmol/l; max. eff. 3.2% micronucleated cells (negative control, 0.9%)	Mäki-Paakanen and Norppa, 1987
mouse lymphoma assay	1.8 to 5 µl/ml	1.9 to 4 µl/ml	pos	with S-9 mix, total growth ranged from 10 to 62%; without S-9 mix, from 5 to 26 %	full report lacking; no data on mutation frequencies; no colony-sizing	Kirby, 1983

Table 5.3 In vitro tests: SCE

	Concentration range					
Test system	With S-9 mix	Without S-9 mix	Result	Toxicity	Remarks	Reference
human lymphocytes	not done	0.1 to 1 mmol/l	pos	strong inhibition of cell proliferation at high doses, but SCE induction not limited to doses with strong toxicity	48-h treatment; pos at all tested doses; extremely steep dose-effect relationship; max. SCE frequency ca. 120 per cell	Norppa et al., 1985
CHO cells	0.2 to 2 mmol/l	0.1 to 5 mmol/l	pos	strong inhibition of cell proliferation at high doses, but SCE induction not limited to doses with strong toxicity	24-h treatment without S-9 mix: strong pos effect at all tested doses; 4 h treatment: stronger effect with S-9 mix than without	Norppa et al., 1985
human lymphocytes	not done	0.1 to 2.4 mmol/l	pos	no data	investigation of time- and dose-dependency: with 1-h treatment doses in the mmol/l-range needed for positive effects; extremely high negative controls of ca. 20 SCE per cell	He and Lambert, 1985

Table 5.4 In vitro tests: DNA strand breaks

	Concentration range					
Test system	With S-9 mix	Without S-9 mix	Result	Toxicity	Remarks	Reference
alkaline elution, human lymphocytes	not done	10 and 20 mmol/l	neg	no data	4-h treatment	Lambert et al., 1985

Table 5.5 In vitro tests: DNA-protein crosslinks

	Concentration range					
Test system	With S-9 mix	Without S-9 mix	Result	Toxicity	Remarks	Reference
DPX, isolated DNA + histone proteins	10 - 100 mmol/l	10 - 100 mmol/l	pos		use of rat liver microsomes instead of S-9 mix; pos only in presence of microsomes	Kuykendall and Bogdanffy, 1992
DPX, cells from rat nasal tissues (respiratory and olfactory)		5 to 75 mmol/l	pos	totally toxic after 2-h exposure to 50 mmol/l	12- to 15-fold increase of DPX levels after 1-2 h exposure; LOEC 25 mmol/l	Kuykendall et al., 1993
alkaline elution, human lymphocytes	not done	10 and 20 mmol/l	pos	no data	the induction of DNA strand breaks by X rays was decreased by treatment with vinyl acetate	Lambert et al., 1985

5.7.2 In vivo data

Table 5.6 In vivo tests: micronuclei (MN) and chromosomal aberrations (CAb) in bone marrow

Test system	Doses	Exposure regimen	Sample time	Result	Local cytotox	General toxicity	Remarks	Reference
MN in mouse bone marrow	250 to 2000 mg/kg	1 x i.p.	30h	pos	500 mg/kg and higher	ca. 50% lethality at 1000 and 2000 mg/kg		Mäki-Paakanen and Norppa, 1987
MN in rat bone marrow	1000 to 5000 ppm	over 3 months in drinking water		neg	no data	no	inappropr. methodology	Gale, 1980a
MN in mouse bone marrow	1000 to 5000 ppm	over 3 months in drinking water		neg	no data	no	inappropr. methodology	Gale, 1980b
MN in rat bone marrow	50 to 1000 ppm	inhalation over 3 months		neg	no data	no	inappropr. methodology	Owen, 1980b
MN in mouse bone marrow	50 to 1000 ppm	inhalation over 3 months		neg	no data	no	inappropr. methodology	Owen, 1980a
CAb in rat bone marrow	160 mg/kg	1 x i.p.	26 h	pos	no data	20% of LD-50	no detailed data	Nersesyan et al., 1990

Table 5.7 In vivo tests: SCE bone marrow

Test system	Doses	Expos. regimen	Sample times	Result	Local cytotox.	General toxicity	Reference
SCE, mouse bone marrow	370 to 560 mg/kg	1 x i.p.	21 h	pos	no	no data	Takeshita et al., 1986

Table 5.8 In vivo tests: DNA binding

Test system	Doses	Expos. regimen	Result	Remarks	Reference
DNA adducts, rat liver	1200 to 1800 ppm	4 h inhalation	neg		Simon et al., 1985
DNA adducts, rat liver	0.1 mmol / animal	1 x orally	neg		Simon et al., 1985

In vivo studies (germ cells)

Table 5.9 In vivo tests: germ cell effects

Test system	Doses	Expos. regimen	Result	General toxicity	Remarks	Reference
MN in early spermatids of mice	250 to 1000 mg/kg	1 x i.p., 13 days recovery	neg	lethality at 750 and 1000 mg/kg	only 1 to 4 mice per group	Lähdetie et al., 1988
sperm abnormality in mice	125 to 1000 mg/kg	daily i.p. for 5 days	pos	lethality at 750 (4/5) and 1000 mg/kg (5/5)	pos 5 weeks after start of treatment, neg at 3 weeks	Lähdetie et al., 1988

5.7.3 Human data

Table 5.10 Human studies: chromosomal aberrations

Test system	Exposure	No. of subjects	Matched negative control	Authors concl.	Genetic effect	Reference
chromos. aberrations in peripheral lymphocytes	not specified	27	no	?	2.2 to 2.5 % (1.0% in negative control)	Shirinian and Arutyunyan, 1980

5.7.4 Other relevant information

5.7.5 Summary and discussion of mutagenicity

Vinyl acetate is negative in bacterial mutagenicity tests.

In mammalian cell cultures various cytogenetic effects were induced in the absence of S-9 mix (chromosomal aberrations, micronuclei, SCE) and in the presence of S-9 mix (SCE; chromosomal aberrations and micronuclei were not analysed with S-9 mix). The lowest positive concentrations ranged from 0.1 to 0.2 mmol/l. A positive mouse lymphoma assay is in line with these results, but it cannot be deduced whether the positive effect is due to chromosomal or to gene mutations (no colony sizing). Mammalian cell culture investigations on DNA strand breaks (DSB) and DNA protein cross-links (DPX) were negative (DSB) or extremely high concentrations were needed for positive effects (DPX).

Very few reliable data are available on the in vivo mutagenicity of vinyl acetate. A weak induction of micronuclei in mouse bone marrow cells was clearly limited to intraperitoneal doses in the LD50 range (1000 and 2000 mg/kg bw). In rats no induction of micronuclei was observed in spermatids (screening assay with intraperitoneal doses up to 1000 mg/kg bw). Further tests on induction of micronuclei or chromosomal aberrations were of too low reliability.

Also in an SCE test with rats positive effects were weak and limited to high and probably highly toxic intraperitoneal doses (370 and 470 mg/kg bw). Such weak increases in SCE frequencies may well be induced by unspecific effects on the cell cycle.

No specific DNA binding was observed in rat livers after inhalation or oral administration.

Induction of sperm abnormalities in mice again was limited to doses in the toxic range. Furthermore, it is not specific for mutagens.

No clear conclusion can be drawn from a human study on the possible induction of chromosomal aberrations in workers exposed to vinyl acetate.

Genotoxicity data on vinyl acetate metabolites are in line with the hypothesis that vinyl acetate genotoxicity is mediated by acetaldehyde. The genotoxicity of acetaldehyde is possibly limited to an overloading of defence mechanisms.

Altogether, vinyl acetate has a mutagenic potential, which is preferentially expressed as clastogenesis. The data on in vivo genotoxicity are difficult to interpret, since their majority is of low reliability, or the effects are not specific to mutagenicity. The most important effect, a weak induction of micronuclei in mouse bone marrow, is limited to intraperitoneal doses of high toxicity. Therefore, it is unlikely that the genotoxic potential of vinyl acetate is expressed in germ cells in man. However, genotoxic effects locally in directly exposed tissues (site of first contact) cannot be excluded; the occurrence and strength of the effects will be dependent on the metabolic capacity of the directly exposed tissue.

No classification of vinyl acetate in terms of germ cell mutagenicity is proposed.

5.8 Carcinogenicity

5.8.1 Carcinogenicity: oral

Species/strain group size	Dose (mg/kg bw, mg/kg diet)	Duration of treatment	Observations and remarks (effects of major toxicological significance)
Rats/ Sprague-Dawley Crl:CD(SD)BR 60 offspring/sex/dose of the main study; 30 offspring/sex/dose as satellite animals	0, 200, 1000, and 5000 ppm Mean daily intake: <u>male:</u> 0, 10, 47, 202 mg/kg bw/d <u>female:</u> 0, 16, 76, 302 mg/kg bw/d drinking water	2 years	The offspring of F0-animals, which received vinyl acetate in drinking water from the time of gestation at target concentrations of 0, 200, 1000 and 5000 ppm, were investigated in a chronic and carcinogenicity study. Vinyl acetate was administered to male and female rats (60 offspring/sex/dose of the main study and 10 offspring/sex/dose for interim sacrifices at week 52 and week 78 and recovery) via drinking water in concentrations of 0, 200, 1000, and 5000 ppm over a period of 2 years. The test substance contained contaminants in concentrations of ≤11.5 ppm acetic acid, ≤71 ppm acetaldehyde, and ≤389 ppm water; the test solution was prepared daily and analyzed at approximately 4-week-intervals. Animals were examined for clinical symptoms, body weight, food and water consumption, parameters of haematology, clinical biochemistry and urinalysis, gross and microscopic abnormalities. Numerous organs were examined histopathologically, but no tissues from the oral cavity (except the tongue) were listed as protocol organs. Rats of the 1000 ppm and 5000 ppm groups consumed less water, and rats at 5000 ppm had decreased food consumption. Mean body weight gain of 5000 ppm males was significantly reduced compared to controls during the first (-11%) and second year (-17%).

Species/strain group size	Dose (mg/kg bw, mg/kg diet)	Duration of treatment	Observations and remarks (effects of major toxicological significance)
			(Cont.) No treatment-related effect was seen for the mortality rates, or the test parameters of haematology, clinical biochemistry or urinalysis. There was no evidence of systemic target organ toxicity. Some organ weights (brain, kidney, heart, liver, spleen, adrenals, pituitary) were altered at ≥1000 ppm, but were not associated with histopathological changes and were therefore considered to be related to lower body weight. The high concentration did not exceed the MTD since feed and water consumption can be attributed to the lower body weight gain. The study authors concluded that there was no treatment-related oncogenic effect. But, squamous carcinomas were seen in the oral cavity of two high dose males and additional single other oral cavity tumours were observed in treated animals (fibrosarcoma in one low and mid dose male each, an odontoma in a mid dose female, and a malignant schwannoma in a high dose female). In addition, a single sarcoma was found in the stomach of a high dose male. All reported tumours (including those in control and treated animals, which were not reported here) were considered to be within normal rates and within the biological variation of this strain and age of rat. Due to the reduced body weight gain at 5000 ppm, the NOAEL for nonneoplastic effects was 1000 ppm (47 mg/kg bw/d in males, and 76 mg/kg bw/d in females). For reason of possible target organs not being routinely examined and the fact that dose-related and significantly increased tumour rates in this study were absent did not give sufficient proof that carcinogenic potential of vinyl acetate was negative. Even when oral cavity was not examined as a protocol organ, two squamous carcinomas were seen in high dose males. As squamous cell carcinomas were not seen in control animals and rarely occur in historical control rats of this strain, it comes into question - due the author's opinion - that this finding may be related to vinyl acetate administration.

Species/strain group size	Dose (mg/kg bw, mg/kg diet)	Duration of treatment	Observations and remarks (effects of major toxicological significance)
			(Cont.) Assumption is supported by concordance with data from other oral cancer studies in rats and mice that reported squamous cell carcinomas in the oral cavity (Umeda et al., 2004). (Bogdanffy et al., 1994a; Shaw, 1988)
Rat/ F344 20/sex/group	0, 1000, 2500 ppm in drinking water	100 weeks	The chronic toxicity study revealed equivocal results concerning higher incidences of tumours in animals after oral administration of vinyl acetate. Groups of 20 male and female rats received vinyl acetate dissolved in drinking water at 0, 1000 or 2500 ppm over a period of 100 weeks and were observed up to 130 weeks. The study performance was inadequate since the vinyl acetate solutions were prepared only once a week, which resulted in hydrolytic degradation. Bogdanffy et al. (1994a) reported a 6% to 14% degradation of vinyl acetate in tap water after 1 day and 40% to 60% over a 7-day period. The group size was small comparing to test standards for carcinogenicity studies and only gross lesions were processed for histopathology. Treatment did not lead to early death of the animals compared to controls. Three types of neoplasm appeared at higher incidences in the treated groups. These were neoplastic nodules in the liver (males: 0/20, 3/20, 2/20; females: 0/20, 0/20, 6/20; historical controls 3-9.1%), adenocarcinomas of the uterus (0/20, 1/20, 5/20; historical controls 0.8%-10.8%), C-cell adenomas and carcinomas of the thyroid gland (males: 2/20, 2/20, 1/20; females: 1/20, 2/20, 6/20; historical controls: 5-7.6%). Data on historical controls were reported from internal control animals and from literature. (Lijinsky and Reuber, 1983)

Species/strain group size	Dose (mg/kg bw, mg/kg diet)	Duration of treatment	Observations and remarks (effects of major toxicological significance)
Rat and mouse Rat/ F344/DuCrj 50 /sex/group Mouse/ Crj:BDF1 50 /sex/group	Rat: 0, 400, 2000, and 10000 ppm Mean daily intake calculated from bw and amount of water consumption: males: 0, 21, 98, 442 mg/kg bw/d; females: 0, 31, 146, 575 mg/kg bw/d) Mouse: 0, 400, 2000, and 10000 ppm Mean daily intake calculated from bw and amount of water consumption: males: 0, 42, 202, 989 mg/kg bw/d; females: 0, 63, 301, 1418 mg/kg bw/d	104 weeks	In a recent carcinogenicity study of the Japan Bioassay Research Center reported to be in conformity to OECD Guideline 453 indicated that higher tumour incidences were induced by oral treatment with vinyl acetate. Groups of 50 male and female rats received drinking water containing 0, 400, 2000, and 10000 ppm vinyl acetate (98%; major impurities: water, acetic acid (no data on ppm), and 5 ppm hydroquinone; test solution was prepared twice a week) for 104 weeks. Groups of 50 male and female mice also received drinking water containing 0, 400, 2000, 10000 ppm vinyl acetate for 104 weeks. The concentrations prepared for each group varied in comparison to the set concentration within a range of 81%-120.8% for the 400 ppm group, 89-102.7% for the 2000 ppm group, and 71.4-112% for the 10000 ppm group in the rat study and for the mice, values ranged from 81-113.3% for the 400 ppm group, 88.4-118.4% for the 2000 ppm group, and 74.1-120% for the 10000 ppm group. The concentrations of vinyl acetate in the drinking water were measured with a gas chromatograph and stability of vinyl acetate in the drinking water was also measured in the preparations around the time of administration of the animals over a four-day period. A comparison of the results was reported to confirm stability (no quantitative data available). During the study, the general condition of the animals was observed once daily, the body weight and food consumption were estimated once weekly for the first 14 weeks, thereafter body weight was checked once per two weeks and food consumption once monthly. For the first 14 weeks water consumption was estimated twice a week and once per two week thereafter.

Species/strain group size	Dose (mg/kg bw, mg/kg diet)	Duration of treatment	Observations and remarks (effects of major toxicological significance)
			(Cont.) Haematology and clinical biochemistry examinations were performed in animals surviving until the time of scheduled necropsy during the 104th week after a fasting period of at least 18 hours. Urinalysis was done on fresh urine collected from the animals as surviving until the last week of administration. At present, no summary tables or individual data are available on laboratory examinations. All animals underwent necropsy at the end of the study (week 97 for the rats, week 94 for the mice); organ weight was measured on scheduled sacrificed animals on brain, lung, liver, spleen, heart, kidney, adrenal, testis, and ovary. During the study the body weight and food consumption were estimated once weekly for the first two weeks, thereafter body weight was checked once per two weeks and food consumption once monthly. For the first two weeks water consumption was estimated twice a week, and once per two week thereafter. Haematology and clinical biochemistry examinations and urinalysis were performed (no data on time). All animals underwent necropsy; organ weight was measured on scheduled sacrificed animals on brain, lung, liver, spleen, heart, kidney, adrenal, testis, and ovary. Histopathology examination of all animals included 37 organs/tissues (including the nasal cavity and the oral cavity with sections on three different levels each on the maxilla and mandible). The vinyl acetate concentrations in the drinking water measured 4 d after the preparations were found to decrease to 72-80% of the initial concentrations for rats and 86-96% for mice. The acetic acid concentration and the pH measured 4 days after the preparation were 9.2 ppm and pH 4.0 for the 400 ppm vinyl acetate-formulated drinking water, 47 ppm and pH 4.2 for the 2000 ppm water and 263 ppm and pH 3.6 for the 10000 ppm water at the end of the 4-day administration period. In the rat, no significant difference between the survival of the treated groups and that of the control group was observed in the males or females. A slight decrease in mean final body weight was observed in the high dose groups (-8% in males, -10% in females) compared to the control groups.

Species/strain group size	Dose (mg/kg bw, mg/kg diet)	Duration of treatment	Observations and remarks (effects of major toxicological significance)
			(Cont.) As outlined in figures on body weight development, the growth curve from week 1 by week 16 was similar for all treatment and control groups. In this group, water consumption was on average 82% for the male rats and 75% for the female rats of that of the control groups. No significant difference in food consumption was seen for male and female groups that received vinyl acetate compared to the control values. Haematology tests reveal elevated concentrations for haemoglobin and MCH in high dose females. Male rats of this group exhibited an elevated albumin/globulin ratio and decreased levels of total cholesterol, phospholipids and calcium. Urinalysis revealed lower urinary pH values in male rats of the 400 ppm and 10000 ppm groups. At necropsy, mandibular nodules were noted in three high dose males and in 1 female from the 400 ppm group in the mandibular region and in the maxillar region of 1 female from the 10000 ppm group. A decrease in the actual weights of the kidneys and livers was noted in male rats received 10000 ppm. There were higher incidences of tumour rates in the oral cavity, oesophagus, and stomach that were considered to be treatment-related. In the oral cavity, increased numbers of squamous cell carcinomas were found in exposed groups of females (control: 0/50, 400 ppm: 1/50, 2000 ppm: 1/50, 10000 ppm: 3/50; with significance $p<0.05$ in the Peto test, not significant in the Fischer's exact test and Cochran Armitage test), a significantly increased incidence occurred in males (control, 400 ppm and 2000 ppm: 0/50, 10000 ppm: 5/50; with significance $p<0.01$ in the Peto test and $p<0.05$ in Fischer's exact test and Cochran Armitage test). Squamous cell carcinoma metastasis to the tongue was noted in 1 male of the 10000 ppm group. Squamous cell papillomas were observed in 2/50 males in the 10000 ppm group (total tumour rate in high dose males 14%). In this dose group, basal cell activation was also observed in 2/50 males and 1/50 females. Epithelial dysplasia was seen in 2/50 of the 10000 ppm females. Mapping of neoplastic and preneoplastic lesions in the rat oral cavity of the high dose group showed that lesions were distributed throughout the cavity, but 4 of 8 carcinomas occurred at level VI (mandibular region at the anterior edge of the lower molar teeth).

Species/strain group size	Dose (mg/kg bw, mg/kg diet)	Duration of treatment	Observations and remarks (effects of major toxicological significance)
			(Cont.) Tumours or lesions presumed to be preneoplastic lesions of the oesophagus and stomach were only evident at 10000 ppm. One female out of 50 had a squamous cell carcinoma of the oesophagus. In 1/50 males and 1/50 females oesophageal squamous cell hyperplasia was observed. In addition, basal cell activation was observed in 4/50 females. No stomach tumours were found, but basal cell activation occurred in 2/50 males and 5/50 females in the 10000 ppm group. Peto test revealed an increasing trend in the occurrence of interstitial cell tumours in the testes of males (control group: 42/50; 400 ppm group: 40/50; 2000 ppm group: 44/50; 10000 ppm group: 47/50), and an increased trend in the occurrence of adenocarcinoma in the mammary glands of females (control group: 0/50; 400 ppm group: 0/50; 2000 ppm group: 0/50; 10000 ppm group: 3/50). Both tumour rates were within the range of historical control data of the testing centre (82-98%, mean 89.6%, for interstitial cell tumours; and 0-6% range, mean 2%, for mammary adenocarcinomas). The increased numbers of squamous cell tumours (malignant and benign) in the oral cavity of male and female rats of the high dose groups were considered as treatment-related. In the context of increased incidences of squamous cell carcinomas of the oral cavity in high dose males and females together with the occurrence of some benign tumours and preneoplastic lesions of this cell type at this dosage and under consideration of the fact that spontaneous tumours of this type and at this site are rare, so it is considered that single squamous carcinomas at 400 and 2000 ppm likely to be associated to vinyl acetate treatment. The same can be assumed for all effects on the oesophagus and stomach. In mice no significant difference between the survival of the treated groups and that of the control group was observed in the males or females. A decrease in final body weight was observed in the high dose groups after week 60 with lower final body weights by 30% in males, and by 18% in females (starting after week 80) compared to the control groups.

Species/strain group size	Dose (mg/kg bw, mg/kg diet)	Duration of treatment	Observations and remarks (effects of major toxicological significance)
			(Cont.) As outlined in figures on body weight development, the growth curve from week 1 by week 12 was similar for all treatment and control group. Decreased mean water consumption was noted in the males of the 10000 ppm group (-15%), and dose-related in all female dose groups (-24% in the 400 ppm group, -8% in the 2000 ppm group, and -17% in the 10000 ppm group, compared to control group values). There was no significant difference in food consumption between treated and control groups. Haematology examinations revealed increased counts of platelets, neutrophils and decreases in lymphocyte counts for high dose males and decreased MCHC for high dose females. Serum glucose was reduced in males of the 400 ppm group and males and females of the 10000 ppm groups. In the males of 10000 ppm group, increased albumin/globulin ratios, increased ALP activity, and decreased total cholesterol, triglyceride and calcium levels were observed. Urinalysis in this group revealed decreased urinary pH values and increased urinary protein, only in females at this dose level increased urinary protein and ketone bodies were noted. Clinical observation revealed tumour masses in the oral cavity in 6 males and 6 females of the 10000 ppm groups, the first appearance was noted in periods between week 65-78 in males and week 92-104 in females. At necropsy, mandibular nodes were seen in 3 males and 5 females, maxillary nodes occurred in 3 males and 1 female in the 10000 ppm groups. Decreases in absolute weights and increases of relative weights of several organs were seen in male and female mice in the high dose groups and the study author thought this to be due to decreased body weight. Tumours associated with the vinyl acetate treatment were observed in the oral cavity, oesophagus, fore stomach and larynx. In the 10000 ppm group, squamous cell carcinomas of the oral cavity occurred in 13/50 males and 15/49 females (both significant) and squamous cell papilloma occurred in 4/50 males and 34/49 females (total incidence of squamous cell tumours in males 32% and in females 37%), but no squamous cell tumours were seen in the control and low dose groups.

Species/strain group size	Dose (mg/kg bw, mg/kg diet)	Duration of treatment	Observations and remarks (effects of major toxicological significance)
			(Cont.) Only at 10000 ppm epithelial dysplasia was observed in 24/50 males and in 17/49 females. From doses at ≥2000 ppm, squamous cell hyperplasia was also observed in 2/50 males and in 1/50 females at 2000 ppm, and in 13/50 males and in 6/49 females at 10000 ppm. Basal cell activation was found in 1/50 males and females each at 2000 ppm and in 18/50 males and 17/49 females at 10000 ppm. More than 60% of the male mice and 35% of the female mice had two or more preneoplastic lesions at different sites of the oral cavity; their incidence was highest at level V of the mandibular region (at the middle point between lower incisor teeth and molar teeth). In the oesophagus, there were squamous cell tumours consisting of carcinomas in 7/50 males and 1/49 females of the 10000 ppm group and of one single papilloma in a 2000 ppm female. In the 10000 ppm group, lesions of preneoplastic nature were epithelial dysplasia (2/50 males, 7/49 females), squamous cell hyperplasia (2/50 males and 2/49 females), and basal cell activation (9/50 males and 15/49 females). In the fore stomach, squamous cell carcinomas occurred in 7/50 males and 3/49 females of the high dose group in comparison to none in the control and other dose groups. Benign squamous cell papilloma was evident in 2/50 males and 1/49 females of this dose group. Males at 10000 ppm had epithelial dysplasia (1/50), squamous cell hyperplasia (3/50), and basal cell activation (1/50). Squamous cell hyperplasia occurred in 2/50 females at 400 ppm and 4/49 at 10000 ppm and basal cell activation was observed in 1/49 females at 10000 ppm. Furthermore, squamous cell carcinomas in the larynx were seen in 2/50 males at 10000 ppm, 1/50 females at 2000 ppm and 1/49 females at 10000 ppm. In this group, there also occurred epithelial dysplasia (2/50 males and 3/49 females), squamous cell hyperplasia (1/50 males) and basal cell activation (3/50 males and 6/49 females).

Species/strain group size	Dose (mg/kg bw, mg/kg diet)	Duration of treatment	Observations and remarks (effects of major toxicological significance)
			(Cont.) The stomach tumours were reported to arise from the fore stomach in treated mice, for basal cell activation of the rat stomach no certain localisation was noted. No other tumour type at any other organ/tissue site increased in both studies. Metastases of squamous cell carcinomas in the oral cavity were found in the lungs and lymph nodes of two males and two females in the 10000 ppm group and in the salivary glands of another female of this group. Squamous cell carcinoma metastases in the lungs with origin from the oesophagus or stomach were also seen in two other males, squamous cell carcinoma in another female metastasised to the kidney, pancreas and lymph nodes. In the 10000 ppm groups, a total of 9 males and 7 females died of tumours in the above mentioned target organs such as oral cavity (6 males and 4 females), in the stomach (1 male and 2 females) or larynx (1 male and 1 female) and in the oesophagus (1 male). The study authors concluded that squamous cell tumours (malignant and benign) occurring in the oral cavity, larynx, oesophagus, and stomach of male and female mice were caused by the administration of vinyl acetate. Atrophy of the salivary glands was noted in 6 males and 4 females in the 10000 ppm group, which were afflicted with tumours on the mandible and was thought to be a secondary change to tumour growth. (Umeda et al., 2004; Celanese, 1998)

Species/strain group size	Dose (mg/kg bw, mg/kg diet)	Duration of treatment	Observations and remarks (effects of major toxicological significance)
Mouse/ Swiss 13-14 m/group 37 f/group Offspring: 37-39 m/group 44-48 f/group	0, 1000, 5000 ppm equivalent to: 0, 150, 750 mg/kg bw/d, calculation based on a water consumption of 15% of body weight drinking water	78 weeks	In a lifetime study on the carcinogenicity of vinyl acetate increased tumour rates in Swiss mice orally treated with vinyl acetate were reported. The study was started in the 80s and the study design did not show conformity with the current guidelines for cancer studies. Daily fresh prepared vinyl acetate solutions were administered in ad libitum supplied drinking water at 0, 1000 or 5000 ppm for 78 weeks. Data on vinyl acetate purity and analytical concentration in the drinking water and on water consumption were not given, but the test substance were reported to contain impurities of benzene (30-45 ppm), methyl and ethyl acetate (50 ppm), crotonaldehyde (6-16 ppm), acetaldehyde 2-11 ppm), and acetone (330-500 ppm). Male and female mice and of male and female offspring were treated starting at 12^{th} day of pregnancy. The animals were submitted daily to a clinical observation, the body weights were registered weekly within the first 13 weeks and every two weeks thereafter until the end of treatment at week 78, and than every 8 weeks until the end of the study. The evidence of gross lesions was checked weekly for the first 13 weeks and thereafter every second week. All animals were necropsied and histopathology was performed on 28 organs/tissues and any other organ with macroscopic lesions. With respect of the presumed target organs, five sections of the head were only included in animals treated longer than 100 weeks. Other target organs such as the tongue, oesophagus, stomach, and intestine were also examined microscopically, but not the larynx. No treatment-related effect on the body weights of male and female breeders and slight decrease in mean body weights in male and female offspring were seen.

Species/strain group size	Dose (mg/kg bw, mg/kg diet)	Duration of treatment	Observations and remarks (effects of major toxicological significance)
			(Cont.) No treatment-related effect on survival rates occurred at the end of the study; the survival rates of the male and female offspring were slightly higher than control animals. It was reported that gross inspection and histological examination observed no behavioural changes or nonneoplastic lesions. Higher incidence of tumours and presumed neoplastic lesions occurred in treated animals in the following organs: Zymbal gland, oral cavity, tongue, oesophagus, fore stomach, glandular stomach, lung, liver, and uterus. The increase of stomach tumours was considered to be a borderline value; higher rates of hepatocarcinomas were only seen among male offspring. The tumours of the lung, liver, uterus and Zymbal gland were not consistent with the findings of the Japanese study. Regarding relatively high spontaneous occurrence of tumours at these sites in the control groups of the study, the interpretation of these results is difficult. As the test substance contained impurities of known carcinogens (e.g. benzene, hydroquinone), the study authors assumed that these impurities were relevant for the tumour response. In spite of reduced reliability of this study due to impure test substance and the non-concordance with guideline testing procedures results provide an indication of neoplastic properties of vinyl acetate, because this study showed consistency with other studies. Compared to control animals that showed normal tissues (except some tongue tumours) there were markedly increased incidences of squamous cell tumour and dysplasia along the exposure route (oral cavity, tongue, oesophagus, and fore stomach). For most effects on the epithelial surface of the upper digestive tract, the offspring were more sensitive than the parent animals. Tumours of this type at these sites were consistent to data from Crj:BDF1 mice in the study of Umeda et al. (2004). The assumption of the authors is considered to be very unlikely, as their concentrations of impurities were extremely low. Based on this study lacking laboratory investigations, the NOAEL for nonneoplastic lesions was 5000 ppm in mice (750 mg/kg bw/d). (Maltoni et al., 1997)

Species/strain group size	Dose (mg/kg bw, mg/kg diet)	Duration of treatment	Observations and remarks (effects of major toxicological significance)
Rat/ Sprague-Dawley Breeder: 13-14m/group 37 f/group Offspring: 53-107 m/group 57-99 f/group	0, 1000, 5000 ppm drinking water	104 week, kept until death	Vinyl acetate was administered in drinking water at doses of 0, 1000 or 5000 ppm to 17-week old Sprague-Dawley rats (breeders) and to 12-day offspring. Treatment was continued for 104 weeks, thereafter animals were kept receiving tap water until their spontaneous death. Vinyl acetate purity was >99%, impurities were benzene 30-45 ppm, methyl and ethyl acetate 50 ppm, crotonaldehyde 6-16 ppm, acetaldehyde 2-11 ppm, and acetone 330-5000 ppm. The study was not compliant to the current standard for a carcinogenicity study. The major limitations were the reduced number of animals tested in the breeders group, the variability of animal numbers among the test groups and the prolongation of the post-treatment period until to the spontaneous deaths. Instead of a study termination animals were aloud to live until their spontaneous death and the tumour incidences were not corrected for the lifetime. No data on food and water consumption were available. There were no differences between treated animals and controls in mean body weight, survival, behaviour, or treatment-related non-oncological pathological changes (no summary data included in the publication). In treatment groups, the rates of total malignancies and carcinomas and/or precursor lesions were increased in oral cavity, lips, tongue, oesophagus, and fore stomach. Tumours of the oral cavity and lips occurred significantly more frequent in offspring males and females (24.5% and 15.5%, respectively, versus 0% in the controls) at 5000 ppm. No significant effect was seen at the end of life in the rat groups (breeders), which were treated from the 17th week onwards. Oral cavity squamous cell carcinomas were seen in two females (5.4%) of the 5000 ppm and in one female of the 1000 ppm (breeders) group. No significant tumour response was seen at the tongue and the oesophagus. Single females of the breeder group at 1000 and 5000 ppm and two females of the offspring group had squamous cell carcinomas of the tongue. However, squamous dysplasia was commonly observed in all treated groups of females, their incidences were significantly higher in the 5000 ppm (breeders and offspring) compared to the controls.

Species/strain group size	Dose (mg/kg bw, mg/kg diet)	Duration of treatment	Observations and remarks (effects of major toxicological significance)
			(Cont.) In the oesophagus, only one squamous cell carcinoma was observed in a male offspring at 5000 ppm. In contrast, the incidences of squamous dysplasia were significantly higher in the breeder and offspring groups at 5000 ppm compared to the control groups. Spontaneous dysplasia in the fore stomach was seen in a number of control animals of the breeders and the offspring (3.7-8.1%). Their rates increased significantly in offspring males and females at 1000 ppm and 5000 ppm (16.1% up to 24.6%). Squamous cell tumours at this site were significantly more frequent in the offspring males at 1000 ppm and 5000 ppm and in the offspring females at 5000 ppm. In conclusion, treatment-related significantly increased rates of tumours were seen in the oral cavity and lips in the 5000 ppm offspring groups of both sexes and in the fore stomach of the offspring groups of male rats at ≥1000 ppm and of female rats at 5000 ppm. Squamous dysplasia considered as precursor lesions were increased in theses groups and also in the breeder groups at 5000 ppm. Although the numbers of animals in the breeders group were limited, the animals of the offspring group at which the treatment started at day 12 of pregnancy appeared to be more sensitive towards tumour and precursor development. (Minardi et al., 2002)

Species/strain group size	Dose (mg/kg bw, mg/kg diet)	Duration of treatment	Observations and remarks (effects of major toxicological significance)
Rat/ Wistar 4-5 males and females/group	0, 100, 200 mg/kg bw/d	3 weeks	The development of hepatic enzyme-altered foci (ATPase, GGTase) was investigated after dosing vinyl acetate to newborn rats for 3 weeks, with or without subsequent promotion by phenobarbital. 3-day-old Wistar (4-5 animals per sex per group) rats were exposed orally to 100 or 200 mg/kg bw/d vinyl acetate (99% pure, impurity: 100 ppm hydroquinone) in condensed milk twice a day for three weeks. Controls received the cream containing 100 ppm hydrochinon only. A subgroup of animals was additionally treated with phenobarbital in drinking water for 8 weeks to stimulate the growth of potentially occurring preneoplastic liver foci. 14 weeks after the start of the study livers were dissected. No ATPase-free and gamma-GT-positive areas in the liver as indication for the development of liver nodules could be found. (Laib and Bolt, 1986)

5.8.2 Carcinogenicity: inhalation

Species/strain group size	conc. mg/l	Exposure time	Duration of treatment	Observations and remarks (effects of major toxicological significance)

Rat and mouse Rat/ Sprague-Dawley Mouse/ CD-1 60 /sex/ dose group 3 satellite groups of 10 of each species and sex for interim evaluation	0 50 200 600 ppm	6 h/day, 5 days/ week	2 years	In a combined chronic toxicity and carcinogenic study male and female rats and mice including 60 animals per sex per dose and three satellite groups of 10 of each species and sex for interim evaluation at week 53 and week 83 and recovery studies (70 weeks of exposure followed by 15/16 weeks of recovery) were exposed by inhalation to vinyl acetate vapour in concentrations of 0, 50, 200 and 600 ppm over a period of 2 years (6 hours/day, 5 days/week). Exposure-related tumour response was observed in the nasal cavity of rats only. Concomitant degenerative, hyperplastic and metaplastic changes of the respiratory tract are described in 5.6.2. A tumour response of other organs related to vinyl acetate treatment was not evident in rats and mice. Rat: A total of 11 nasal cavity tumours classified as papilloma, squamous cell carcinoma, carcinoma in situ in olfactory regions, and papilloma and squamous cell carcinoma in respiratory or anterior non-olfactory regions were evident in 7 males (11.9%) and 4 females (6.7%) of the high dose rat group. In the intermediate dose groups a single tumour (benign papilloma of the olfactory region) was found in a male rat. In the larynx a squamous cell carcinoma was found in a high dose female. No treatment-related tracheal or lung tumour was observed. No respiratory tract tumour was seen in the control and low dose groups except a single adenoma of the lung in a control female. In mice, no treatment-related increased incidence of tumours was observed in the nose, larynx, trachea, lung, or other tissues of mice in the main study and in the satellite groups. A single squamous cell carcinoma in a major lung bronchus of a high dose male and a single adenocarcinoma in the lung of a control male were noted. (Owen, 1988; Bogdanffy et al., 1994b)

5.8.3 Carcinogenicity: dermal

No data available.

5.8.4 Carcinogenicity: human data

In a cohort study, 4806 male workers who were exposed to 19 different chemicals (vinyl chloride, polyvinylchloride dust, chlorinated solvents, acrylates, acrylonitrile and others) including vinyl acetate, between the years 1942 and 1973 had an excess risk of cancer of the respiratory system and the CNS. A subgroup (of cases with lung cancer) with undifferentiated large cell lung cancer was associated to a slightly higher cumulative exposure to vinyl acetate (Waxweiler et al., 1981).

A nested case-control study was undertaken in a cohort of 29139 men employed in two chemical manufacturing facilities and a research and development centre, who had died in 1940-1978 with non-Hodgkin`s lymphoma, multiple myeloma, lymphocytic or non-lymphocytic leukaemia. Exposure odds ratios (OR) were examined in relation to 111 work areas, 21 specific chemicals (OR based on an ever/never basis), and 52 chemical activity groups. Exposure to vinyl acetate was associated with non-Hodgkin`s lymphoma in seven of 52 men (OR 1.2), multiple myeloma in three of 20 men (OR 1.6), non-lymphocytic leukaemia in two of 39 men (OR 0.5), and with lymphocytic leukaemia in two of 18 men (OR 1.8). Examination of OR related to the exposure duration was not done because of the OR <1.3 or number of cases <4 (Ott et al., 1989).

5.8.5 Other relevant information

5.8.6 Summary and discussion of carcinogenicity

Data summary

Data on human experience were not specifically associated to the exposure with vinyl acetate. In summary, the above-mentioned epidemiological data are insufficient to evaluate the carcinogenic potential of vinyl acetate in humans.

In rats, vinyl acetate induced an increased number of nasal tumours (mainly papillomas and squamous cell carcinomas) in various regions of the nasal mucosa after long-term inhalation. The total incidence was significantly increased at a concentration of 600 ppm, but a single papilloma already developed at 200 ppm. No significant tumour response was seen in mice after long-term inhalation of vinyl acetate vapour. Occasionally single squamous cell tumours occurred at other sites of the respiratory tract in rats and mice.

Although the complete report was not available, published information on an oral cancer study in F344 rats and BDF1 mice (Umeda et al., 2004) demonstrated significantly increased rates of squamous cell tumours in the oral cavity (rats and mice), oesophagus and fore stomach (mice) after a 2-year administration of 10000 ppm vinyl acetate with the drinking water (equivalent mean doses in rats were 442 mg/kg bw/d for males, 575 mg/kg bw/d for females, in mice 989 mg/kg bw/d for males, 1418 mg/kg bw/d for females). Maximum increase in tumour incidences was found in the oral cavity in both species. Squamous cell carcinomas were already observed at a dose of 400 ppm in female rats (31 mg/kg bw/d). Consistently in another life-time study on a breeding and offspring generation of mice (Maltoni et al., 1997), which did not met actual standards on cancer bioassays, squamous cell tumours were also observed with increased incidences in several sites of the gastrointestinal tract (oral cavity, tongue, oesophagus, fore stomach) at a concentration of 5000 ppm in the drinking water (calculated dose 780 mg/kg bw/d). In addition, higher incidences of adenocarcinomas of the glandular region of the stomach were found in high-dose male breeders.

Also some other organs (lung, liver, and uterus) showed increased rates of benign and malignant tumours compared to that of the control groups. Tumours of the liver and the uterus have also been seen in the Lijinsky study (Lijinsky and Reuber, 1983). However, both studies hampered from methodical insufficiencies. Further, these data were inconsistent to the absence of parenchymal tumours in other more valid studies. Therefore interpretation of these tumours remains unclear.

No clear positive tumour response was found in another oral rat cancer study at vinyl acetate concentrations up to 5000 ppm (Shaw, 1988; Bogdanffy et al., 1994a). However, except the tongue, tissues of the oral cavity were not included as standard protocol tissues for histopathology. But, this study showed the occurrence of two squamous cell carcinomas in the oral cavity of males of the 5000 ppm group.

Published data on rats exposed to drinking water containing 1000 ppm or 5000 ppm vinyl acetate confirmed significant increases in squamous cell carcinomas of the oral cavity and the fore stomach (Minardi et al., 2002). Treatment of offspring resulted in higher tumour rates than in rats with treatment begin at week 17 of life. However, this study has a number of limitations in its design. Thus, tumour response along the gastrointestinal could be interpreted to be supportive to the results from the Umeda study.

Based on concentration tested in experimental studies, continuous exposure to vinyl acetate has the potential to cause tumours in animals at the site of first contact. Three major target sites were identified from inhalation and oral studies: the olfactory region of the nasal mucosa, the non-olfactory (respiratory) region of the nasal mucosa and the mucosa of the upper gastrointestinal tract.

The present knowledge on the mode of action by which vinyl acetate induces local tumour growth at contact sites is separately considered for each of the main target sites. A comprehensive discussion on the mode of action for vinyl acetate is included in the EU RAR (2008).

Actual considerations on the assessment of the mode of action for tumours of the respiratory tract:

Acetaldehyde is the critical metabolite with a carcinogenic potential.

The distribution and capacity of enzymes responsible for vinyl acetate toxicification and detoxification are of major importance to create a preliminary understanding of the modes of carcinogenic action. The present understanding is that acetaldehyde plays a critical role in the tumourigenicity of vinyl acetate.

The principal similarities of toxic and carcinogenic effects of vinyl acetate to those of acetaldeyhde suggest that the hydrolysis product acetaldehyde is the active carcinogenic metabolite of vinyl acetate.

Acetaldehyde is a biological constituent of many cells and is – beside the release from the man-made sources - ubiquitarily present in many foods and natural sources. Exposure to vinyl acetate induces concentration-related increases in intracellular concentrations of the hydrolytic products acetaldehyde and acetic acid. Efficiency of the absorption is optimal at lowest concentrations and decreases with increasing concentration (see 4.1.2.1 in the EU RAR 2008). Increasing concentrations of the vinyl acetate may result in an accumulation of acetaldehyde when the cellular detoxification capacity of aldehyde dehydrogenase is overwhelmed. The toxicity and/or carcinogenicity reflect the function of metabolic capacity of the target epithelium. The specific regional and cellular susceptibility to cytotoxicity corresponds to the distribution and activity of the enzymes involved.

Acetaldehyde is thought to be the responsible metabolite for the genotoxic effects seen in mammalian cell cultures on vinyl acetate.

A hypothesis of a cytotoxicity-related carcinogenesis is likely to induce tumours in the olfactory region.

- The rat olfactory tissue efficiently catalyses the formation of acetaldehyde and acetic acid.
- Absorption and metabolic transformation of vinyl acetate by carboxylesterase is a concentration dependent process. Due to the absent or low aldehyde dehydrogenase activity (as compared to the carboxylesterase activity) only low concentrations of acetaldehyde can be oxidised. Above a yet non-identified exposure concentration, the production of acetaldehyde exceeds further oxidation, which results in an intracellular accumulation of acetaldehyde.
- Acetic acid-related cytotoxicity following vinyl acetate hydrolysis appears to be the initial event in tumourigenicity for tumours with origin in the olfactory epithelium.
- A direct genotoxic action of the metabolite acetaldehyde on the restorative epithelium could contribute to tumour initiation.
- Cell death induces increased cell turn over of surviving cells or basal cells. DNA synthesis is elevated and the incidence of genotoxic effects is expected to increase.

In conclusion, it appears plausible to explain the sequential steps from cytotoxicity to carcinogenesis for the olfactory epithelium. The sites of epithelial damage correlated with increased cell proliferation as evidenced by basal cell hyperplasia and transformation to squamous metaplasia. The latter was considered to be a precursor lesion of benign and malignant tumours that were squamous cell papillomas and carcinomas.

The contribution of intracellular acidification as the initial step leading to cytotoxicity and thereby to carcinogenicity remains uncertain. Short term testing indicated that the degree of intracellular acidification was only minor and reversible. Also, the site-specific changes in intracellular acidification as predicted in the PBPK-model (Plowchalk et al., 1997) were not consistent with the in-vivo preference of cytotoxicity. Genotoxicity data indicate a possible genotoxic effect of vinyl acetate mediated by its metabolite acetaldehyde, which may contribute to the tumour development at concentrations, which were cytotoxic.

At present, a narrative for a threshold concentration for tumour development could be identified for the olfactory region by its cytotoxicity.

A threshold mode of action is thought to be active for tumours with origin in the other nasal regions.

For the other (non-olfactory) tumour sites of the upper respiratory tract (mainly the nasal respiratory epithelium), cytotoxicity was clearly not a critical event in tumour formation, because tumours occurred at lower exposure concentrations than cytotoxicity. The predictions from the PBPK model, with respect to the degree of acidification and thereby of the cytotoxic response did not reflect the observed study data. During the last years, scientific working groups recognised the lack of evidence for the early proposals on acidification as the relevant mode and introduced considerations about the role of intracellular acidification in stimulation of cell growth and transformation (Lantz et al., 2003). These secondary responses occur only at higher doses.

The following aspects support the hypothesis of a threshold mode of action:

- Absorption and metabolic transformation of vinyl acetate is a concentration dependent process.
- Carboxylesterase activity in the respiratory epithelium is at least half than that of the olfactory epithelium in man and rats. The hydrolysis rates of vinyl acetate and thereby the intracellular concentrations of acetic acid and acetaldehyde are expected to be markedly lower than in the olfactory epithelium.
- Aldehyde dehydrogenase (ALDH) is the key enzyme for the elimination of acetaldehyde. Its activity is more than 2fold higher in the respiratory epithelium than in the olfactory epithelium. The enzyme activity is sufficient to cope with low concentrations of vinyl acetate and its produced metabolite acetaldehyde. At high concentrations of intracellular acetaldehyde ALDH activity will not be sufficient to oxidise all acetaldehyde to acetic acid and acetaldehyde may accumulate. Saturation of the metabolism of acetaldehyde by ALDH indicating limited enzyme capacity is suggested to occur at acetaldehyde concentrations of 300 ppm (Stanek and Morris, 1999).
- No toxicity was observed in respiratory epithelium up to 600 ppm in 2-year studies. Regarding acetic acid as the cytotoxic metabolite, acetic acid generation at 600 ppm is below the threshold for cytotoxicity.
- No increase in proliferative activity either measured as proliferation index or as hyperplastic/metaplastic changes up to 600 ppm vinyl acetate in (LOAEC 1000 ppm). It is assumed that increased cell proliferative activity is acetaldehyde-related. As no cytotoxicity or other relevant effect was seen up to 600 ppm, no significant intracellular concentration of acetaldehyde is expected to occur.
- In accordance to data from oral studies on mitogenic action of vinyl acetate a mitogenic action could be assumed above a threshold concentration. Due to the lack of adequate studies on the respiratory tract, evidence from studies on gastrointestinal tract was considered: Basal cell hyperplasia and epithelial hyperplasia in the gastrointestinal tract without preceding cytotoxicity were evident at ≥10000 ppm (NOAEL 5000 ppm ≈1200 mg/kg/d, 92-day mouse study; Valentine et al., 2002).
- Tumour response was seen at ≥600 ppm vinyl acetate, no tumours were observed at concentrations below.
- It is assumed that acetaldehyde-caused genotoxicity is active at vinyl acetate concentrations that cause acetaldehyde accumulation.
- The toxicological relevance of minimal reduction in pH remains questionable.
- Actually, an exact threshold concentration for acetaldehyde accumulation could not be estimated for the non-olfactory region.
- Since no biological response in the respiratory mucosa was observed in long-term inhalation studies up to 200 ppm vinyl acetate exposure, it is concluded that the cellular integrity is not disrupted.

Table 5.11 Critical steps in vinyl acetate (VA) tumour formation in the respiratory tract

VA Absorption ⇩		
Metabolism of vinyl acetate to acetaldehyde and acetic acid in:		
Olfactory epithelium Sustentacular cells + neuronal (sensory) cells: Carboxylesterase activity +++ ALDH activity - ⇩	Olfactory epithelium Basal cells + Bowman's glands: Carboxylesterase activity +++ ALDH activity (+) ⇩	Respiratory epithelium Respiratory epithelium cells: Carboxylesterase activity + ALDH activity +++ ⇩
High acetaldehyde production No detoxification of acetaldehyde Intracellular accumulation of acetaldehyde Cytotoxicity at 200 ppm ⇩	High acetaldehyde production Very limited detoxification of acetaldehyde Intracellular accumulation of acetaldehyde ⇩	Limited acetaldehyde production A: Up to a threshold concentration: Efficient detoxification though high ALDH capacity No toxic effect up to 200 ppm B: Above threshold concentration: Imbalance of acetaldehyde production and detoxification Intracellular accumulation of acetaldehyde ⇩
Secondarily to cytotoxicity of the primary target cells: Restorative cell proliferation of surviving basal cells Replacement by respiratory-like epithelium and squamous cell metaplasia ⇩		Cell proliferation due to direct mitogenic effect ⇩
Genotoxic effects of acetaldehyde on proliferating cells (inclusive tumour relevant genes) Tumour initiation and development Tumour response: LOAEC 600 ppm Cytotoxicity: LOAEC 200 ppm/NOAEC 50 ppm		Genotoxic effect of acetaldehyde on proliferating cells (inclusive tumour relevant genes) Tumour initiation and development Tumour response: LOAEC 600 ppm/NOAEC 200 ppm

ALDH: aldehyde dehydrogenase

Actual considerations on the assessment of mode of action for tumours of the gastrointestinal tract:

Based on the actual information, the previous assumption of cytotoxicity-mediated carcinogenicity of vinyl acetate was considered not to be plausible for the gastrointestinal tract. Up to now, the link between observed cytotoxicity and tumours in the gastrointestinal tract of animal studies supporting the postulated mode of action is missing. Therefore, the contribution of other mode of actions has been considered. Although the overall database is much less than for the inhalation route there are similarities among the tumour sites.

Acetaldehyde is the critical metabolite with a carcinogenic potential.

Although carboxylesterase activity is low in the epithelium lining of the gastrointestinal tract, acetaldehyde is thought to be significant for tumour development. The high test concentrations needed to induce tumour response are thought to be reflective of the low hydrolytic activity.

A threshold mode of action is assumed to be active in the tumour development in the gastrointestinal tract.

Vinyl acetate is hydrolysed by the mucosal carboxylesterase to acetic acid and acetaldehyde.

Due to the fact that cytotoxicity could be ruled out as a precedent lesion and considering that the metabolism is in principle comparable to the nasal regions the pathways of tumour development in the upper gastrointestinal tract is expected to be comparable to the non-olfactory (respiratory) regions.

Acetaldehyde is oxidised by aldehyde dehydrogenase. The enzyme activity will be high enough for the oxidation of the physiological concentrations of acetaldehyde. As significant increases in tumour response were seen at rather high concentrations of vinyl acetate: 10000 ppm for rat and mouse (Umeda et al., 2004), ≥5000 ppm for mice (Maltoni et al., 1997), 1000 ppm for the rat (Minardi et al., 2002); enzyme activity might cope for the low concentrations of produced acetaldehyde without any harmful effect on cell viability and integrity. However, it is unlikely that there is enough activity for effective acetaldehyde oxidation at high concentrations of vinyl acetate; and acetaldehyde may accumulate.

Accumulated acetaldehyde produces genotoxic effects.

High concentrations of vinyl acetate are mitogenic. A dose-related increase of cell proliferative activity increased dose-related above 10000 ppm in mice (≥2300 mg/kg bw/d), no effect was seen at 5000 ppm. In rats, a less than 2-fold increase in proliferative activity was observed at 24000 ppm in rats (1400 mg/kg bw/d).

Cytotoxicity was not obvious up to tumour-inducing concentrations and therefore could be ruled out as a precedent change in the tumour development. The cleavage product acetic acid is also discussed to induce intracellular acidification. A reduction of intracellular pH was also seen for buccal mucosa. As for the nasal mucosa the extent of pH-reduction is low, which raises the question on the significance of this low range shift in intracellular pH.

The exact concentration of vinyl acetate where production of acetaldehyde and its removal starts to be imbalanced could not be estimated by data available. It is therefore proposed to select the most sensitive biological effect with putative toxicological relevance as a starting point to estimate a threshold. Since no clear NOAEL could be determined from the carcinogenicity studies, the vinyl acetate concentration (400 ppm) inducing the single tumours in the rat oral cavity were chosen as the LOAEL.

Conclusion

Vinyl acetate exposure produced tumours at the site of first contact along the exposure routes. A threshold mode of carcinogenic action is thought to be active. The observed tumour responses are reflecting the target site-specific enzyme activities.

Following inhalation and oral exposure vinyl acetate is rapidly 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. Intracellular aldehyde dehydrogenase activity is limited, at higher concentrations of vinyl acetate it will not be sufficient for the oxidation of generated acetaldehyde. Thus, at high vinyl acetate concentrations non-physiologically high concentrations of acetaldehyde are produced. Acetaldehyde is a physiological intermediate with low background concentrations. Its adverse effects (genotoxicity and mutagenicity) are limited to non-physiologically high concentrations. Therefore, a threshold mode of action is assumed for vinyl acetate.

Above threshold concentrations, cytotoxicity (only at the olfactory mucosa), mitogenic actions and genotoxic actions occurred.

Cytotoxicity mainly contributed to acetic acid is the earliest lesion in the olfactory mucosa. Next stages in the continuum to tumour development include the responsive restorative cell proliferation and simultaneously occurring genotoxic effects of acetaldehyde.

Increased cell proliferative activity was observed at high concentrations of acetaldehyde or vinyl acetate. Its occurrence was not linked to cell toxicity as a precondition.

The systemic bioavailability of vinyl acetate or its metabolite is very low (EU RAR 2008). In vivo genotoxicity tests showed that systemic genotoxicity appears to be limited to toxic doses. This is in line with the absence of systemic carcinogenic effects.

Data on vinyl acetate are in line with the idea that vinyl acetate genotoxicity is mediated by acetaldehyde. Increasing concentrations of acetaldehyde produce genotoxic actions at the site of contact. It has to be taken into consideration that acetaldehyde occurs naturally in mammalians cells and is part of the physiological cellular metabolism.

The threshold concentration leading to acetaldehyde accumulation could not yet be estimated. Using in vitro test systems as a surrogate for a site of contact model, in vitro data for several genotoxic endpoints are suggesting for a threshold concentration above which acetaldehyde exerts its genotoxic action. A NOAEC of 0.1 mmol/l for chromosomal aberrations and 0.03 mmol/l for SCE was determined. Since for the in vivo situation no biomarker for the limitation of acetaldehyde oxidation is available, it is proposed to use the identified NOAEC, respectively the LOAEL from the most sensitive biological effects as a surrogate to derive a threshold concentration for risk characterisation purposes.

Overall, it is considered that the critical events in vinyl acetate carcinogenesis do fit to the criteria for the exceptional cases where genotoxic action is thought to be thresholded[1].

From animal data it is concluded that vinyl acetate might pose a cancer risk for humans exposed to the substance via the inhalation or oral route. Carcinogenicity is thought to act via a secondary mechanism and the concern may only be relevant above threshold concentrations.

The observed effects are thought to be relevant for the human. For the respiratory tract humans may be less sensitive than the rat due to a lower carboxylesterase activity in the nasal mucosa.

Proposal for classification

An extended analysis of the weight of evidence is found in EU RAR 2008. In short, the justification for classification is summarised as:

There is no adequate database on humans.

Relevant cancer studies for the classification proposal were Owen (1988), Bogdanffy et al. (1994b), Umeda et al., (2004), Minardi et al. (2002) and Maltoni et al. (1997). Test concentrations in these studies did no exceed the MTD.

Vinyl acetate was carcinogenic in two animal species each at both sexes.

Carcinogenic potential was demonstrated for two administration routes: inhalation and oral.

Vinyl acetate was carcinogenic at the site of first contact, the surface epithelium along the exposure routes.

Spontaneous rates of nasal tumours and epithelial tumours from the upper and lower airways and from the upper gastrointestinal tract in the test species used are known to be very low.

All target organs of tumour development were considered to be relevant for humans.

No species-specific mode of action for vinyl acetate carcinogenesis was identified.

The carcinogenic effect of vinyl acetate is thought to be related to genotoxic activity of the metabolite acetaldehyde. Comparable tumour findings and genotoxicity data from acetaldehyde support this assumption.

A threshold mechanism is thought to be active. Tumour development is reflecting the target site-specific enzyme activities involved in the hydrolysis of vinyl acetate and the metabolism of acetaldehyde. At higher concentrations the enzyme activities will not be high enough for the oxidation of generated acetadehyde. Then acetaldehyde accumulates intracellularly and is causing

[1] Technical Guidance Document on Risk Assessment, Human Health Risk Characterisation (EC TGD 2003, http://ecb.jrc.it/tgdoc)

There are two general cases where mutagenicity may be shown to have a threshold:

(2) where the toxico-kinetic considerations clearly demonstrate that mutagenic metabolites will only be produced in vivo at very high exposures to the parent substance which are unlikely to be achieved in realistic human exposure scenarios. For example, where the active metabolite is only produced by a metabolic pathway that occurs when other preferential pathways are saturated, or where there is very rapid removal of the active metabolite by conjugation or detoxification, such that no biological significant amounts reach the DNA in vivo, except when these pathways are overwhelmed.

increased cell proliferative activity, increased DNA adduct formation and DNA damage (clastogenicity). Cell proliferative activity of acetaldehyde and DNA adduct formation are only active above certain (threshold) concentrations.

As for acetaldehyde, mitogenic action was seen at high local concentrations of vinyl acetate. 10000 ppm or higher concentrations of vinyl acetate produced proliferative hyperactivity in mice whereas no such effect was observed at concentrations up to 5000 ppm. The exact mechanisms how the mitogenic response is initiated are unknown.

Cytotoxicity was assumed as one contributing mode of carcinogenesis in the olfactory mucosa diminishing the resistance of the olfactory mucosa due to its site-specific high carboxylesterase activity and the low aldehyde dehydrogenase activity. The consistent dose-response and time-response relationships between cytotoxic effect and tumour growth support this assumption.

In the olfactory epithelium a multistage hypothesis of carcinogenesis is likely to be based to initial cytotoxicity, responsive cell proliferation and associated with genotoxic action of its metabolite acetaldehyde.

For the other tumour sites, the non-olfactory (respiratory) epithelium as well for the mucosa of the upper gastrointestinal tract, concentration-dependent increased cell proliferation coupled with the genotoxic action of acetaldehyde at high concentrations of acetaldehyde were assumed to result in tumour development.

For the inhalation route, cytotoxicity in the olfactory mucosa is the most sensitive effect related to the tumour response and is therefore taken for quantitative risk assessment. Cytotoxicity and related reparative cell proliferation are assumed to be early events in the tumour development in this region. A NOAEC of 50 ppm established for the cytotoxic effects in the olfactory mucosa is proposed to be used as a threshold concentration. For the oral route, the lowest tumour dose (400 ppm corresponding to 21 mg/kg bw/d) is proposed as basis to calculate a threshold concentration.

According to the Annex VI criteria given in Directive 67/548/EEC vinyl acetate should be classified and labelled as Carc. Cat. 3; Harmful, Xn; R40 (Limited evidence of a carcinogenic effect). This corresponds to Carc. 2 H351 (Suspected human carcinogen) according to CLP Regulation (2008).

5.9 Toxicity for reproduction

Not evaluated for this dossier.

5.9.1 Effects on fertility

5.9.2 Developmental toxicity

5.9.3 Human data

5.9.4 Other relevant information

5.9.5 Summary and discussion of reproductive toxicity

5.10 Other effects

Not evaluated for this dossier.

5.11 Derivation of DNEL(s) or other quantitative or qualitative measure for dose response

Not relevant for this type of dossier.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

6.1 Explosivity

No experimental data on explosive properties:
Testing can be waived based on a consideration of the chemical structure in accordance with REACH Column 2 of Annex VII, section 7.11:
The classification procedure needs not to be applied because there are no chemical groups present in the molecule which are associated with explosive properties.

No classification for explosivity is proposed.

Thermal stability:

The monomer is volatile and tends to self-polymerrise, and is therefore stored and handled cool and inhibited, with storage limited to below 6 month.

Vinyl acetate is normally inhibited with hydroquinone to prevent polymerisation. A combination of too low level of inhibitor and warm, moist storage conditions may lead to spontaneous polymerisation. This process involves autoxidation of acetaldehyde (a normal impurity produced by

hydrolysis of the monomer) to a peroxide which initiates exothermic polymerisation as it decomposes.

[1] P. G. Urben (Ed.): *Bretherick's Handbook of Reactive Chemical Hazards*, 7th ed., Elsevier 2007.

Vinyl acetate, unstabilised, is proposed to classify additionally with R19/EUH019.

6.2 Flammability

Vinyl acetate meets the classification criteria as highly flammable liquid: The flash point measured in a closed cup is -8 °C and with a boiling point at 72.7 °C.

Vinyl acetate forms explosive mixture with air (explosion limits in air (vol%) 2.6 to 13.4; autoignition temperature 385 °C).

Pyrophoric properties: The classification procedure needs not to be applied because the organic substance is known to be stable into contact with air at room temperature for prolonged periods of time (days).
Flammability in contact with water: The classification procedure needs not to be applied because the organic substance does not contain metals or metalloids.

Proposed classification based on Directive 67/548/EEC:
F, R11 Highly flammable

Proposed classification based on Regulation (EC) No 1272/2008:
Flam. Liq. 2; H225 Highly flammable liquid and vapour

6.3 Oxidising potential

No experimental data on oxidising properties:
Testing can be waived based on a consideration of the chemical structure in accordance with REACH Column 2 of Annex VII, section 7.13: The classification procedure need not to be applied because the organic substance contains oxygen, which is chemically bonded only to carbon.

No classification for oxidising properties is proposed.

7 ENVIRONMENTAL HAZARD ASSESSMENT

Not evaluated for this dossier.

JUSTIFICATION THAT ACTION IS REQUIRED ON A COMMUNITY-WIDE BASIS

Vinyl acetate was a priority substance in the existing chemical program (EEC) 793/93, but the work was not finished by 1 June 2008. The proposal to classify vinyl acetate as Carc. Cat. 3; R40, Xn; R20, and Xi; R37 was already submitted to TC C&L and was agreed on in September 2007 based on the data summarised in the EU RAR 2008. The corresponding classification in accordance with CLP Regulation 2008 is Carc. 2 H351, Acute Tox 4 H332, and STOT Single 3 H335.

Action on a community-wide basis is required to finalise the harmonised classification and labelling under Regulation (EC) No 1272/2008 (REACH).

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