Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at Community level of

vinyl acetate

ECHA/RAC/DOC No CLH-O-0000001742-77-01/F

Adopted

10 June 2011

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OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT COMMUNITY LEVEL

In accordance with Article 37 (4) of the Regulation (EC) No 1272/2008 (CLP Regulation), the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling of

Substance Name: ***Vinyl acetate***

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

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

The proposal was submitted by ***Germany***
and received by RAC on **20 August 2011**

Harmonised classification originally proposed by the dossier submitter:

	CLP Regulation (EC) No 1272/2008	Directive 67/548/EEC (criteria)
Current entry in Annex VI CLP Regulation	Flam. Liq. 2; H225 Note D	F; R11 Note D
Original proposal by dossier submitter based on the outcome of discussions at the Technical Committee on Classification and labelling (TC C&L) for consideration by RAC	Flam. Liq. 2; H225 Carc. 2; H351 Acute Tox. 4; H332 STOT SE 3; H335	F; R11 Carc. Cat. 3; R40 Xn; R20 Xi; R37
Subsequent proposal (submitted by dossier submitter after the accordance check for public consultation) Part A: Vinyl acetate in a stabilized form	Carc. 2; H351 Flam. Liq. 2; H225 Acute Tox. 4; H332 STOT SE 3; H335	Carc. Cat. 3; R40 F; R11 Xn; R20 Xi; R37
Subsequent proposal (submitted by dossier submitter after the accordance check for public consultation) Part B: Vinyl acetate in a not-stabilized form	Carc. 2; H351 Flam. Liq. 2; H225, Acute Tox. 4; H332 STOT SE 3; H335 EUH019	Carc. Cat. 3; R40 F; R11, R19 Xn; R20 Xi; R37 Note D

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

PROCESS FOR ADOPTION OF THE OPINION

Germany has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/consultations/harmonised_cl/harmon_cl_prev_cons_en.asp*** on ***20 August 2010***. Parties concerned and MSCAs were invited to submit comments and contributions by ***4 October 2010***.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: ***Helena Polakovicova***
Co-rapporteur, appointed by RAC: ***Andrew Smith***

The opinion takes into account the comments of MSCAs and other parties concerned provided in accordance with Article 37 (4) of the CLP Regulation.

The RAC opinion on the proposed harmonised classification and labelling has been reached on ***10 June 2011,*** in accordance with Article 37 (4) of the CLP Regulation, giving parties concerned the opportunity to comment. Comments received are compiled in Annex 2.

The RAC Opinion was adopted by ***consensus***

OPINION OF RAC

The RAC adopted the opinion that the current harmonised classification of vinyl acetate (with Note D) should be amended to read as follows:

Classification & Labelling in accordance with the CLP Regulation:

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
607-023-00-0	Vinyl acetate	203-545-4	108-05-4	Carc. 2 Flam. Liq. 2 (currently in Annex VI) Acute Tox. 4 STOT SE 3	H351 H225 H332 H335	GHS02 GHS07 GHS08 Dgr	H351 H225 H332 H335			D (currently in Annex VI)

Classification & Labelling in accordance with Directive 67/548/EEC:

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
607-023-00-0	Vinyl acetate	203-545-4	108-05-4	Carc. Cat. 3; R40 F; R11 (currently in Annex VI) Xn; R20 Xi; R37	F; Xn R: 11-20-37-40 S: (2-)36/37-46		D (currently in Annex VI)

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

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

RAC was of the opinion that this single entry for vinyl acetate, with Note D would, as currently, be adequate to cover the potential for this substance to be supplied in a stabilised or non-stabilised form.

SCIENTIFIC GROUNDS FOR THE OPINION

Substance for which a harmonised classification and labelling has previously been agreed at TC C&L

For vinyl acetate, TC C&L in September 2007 agreed to a harmonised C&L in accordance with a proposal from Germany that added classifications for acute toxicity, respiratory tract irritancy and carcinogenicity to the Annex I entry under Directive 67/548/EEC. No change to the classification for flammability was proposed, and no classification for environmental effects was considered necessary. An identical proposal was submitted by Germany in the present CLH dossier, but with the additional complexity of proposing 2 separate entries for vinyl acetate in stabilised form (without Note D) and non-stabilised form (with Note D and labelling for the possibility of explosive peroxide formation), respectively.

No new data were added since the discussion by the TC C&L in September 2007, including during the public consultation period.

The responses from the public consultation suggested that different approaches are foreseen in industry and by certain Member States regarding the application of Note D. It was questioned whether EUH019/R19 was applicable for harmonised classification. During the plenary discussion held at RAC15, the rapporteur proposed that a single entry in Annex VI seemed to be the most appropriate way forward. This would include the new human health effects classification previously agreed by TC C&L, which was supported by those who commented during the public consultation. This entry would also maintain the application of Note D and accordingly leave open the possibility of adding EUH019/R19 for vinyl acetate if supplied in non-stabilised form. This was judged adequate to cover the potential for this substance to be supplied either in a stabilised or non-stabilised form.

The rapporteur noted that labelling for the possibility of explosive peroxide formation when a substance is supplied in non-stabilised form is not considered as a priority under CLP; it is not a “harmonised endpoint”.

During the first round of commenting by RAC members, there were no disagreements with the proposed way forward.

This Opinion relates only to those hazard classes that have been reviewed in the proposal for harmonised classification and labelling, as submitted by ***Germany***.

The Background Document, attached as Annex 1, provides detailed scientific grounds for this Opinion. The following summary corresponds to the endpoint-related “summary and discussion” chapters of the Background Document.

Acute toxicity

The German proposal related specifically to inhalation toxicity, and the following text is reproduced directly from the appropriate summary and discussion section of the submitted report.

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; R20 (67/548/EEC; DSD) (Annex VI: LC_{50}, vapours: 2 – 20 mg/l/4hr). This corresponds to Acute Tox. 4; H332 (CLP) (Annex I, Part 3, 3.1 Acute toxicity, Category 4, vapours: 10.0 < ATE ≤ 20.0 mg/l/4hr).

RAC Opinion

The evaluation by RAC relates to the classification proposal of the dossier submitter, whose proposal was in line with the agreed TC C&L recommendation and was not questioned during public consultation.

Inhalation toxicity testing resulted in LC_{50} values of 15.8 mg/l/4h and 14.1mg/l/4hours in rats. These values lie within the ranges that justify classification with Acute Tox 4; H332 (CLP) and Xn; R20 (DSD). RAC accepted this proposal of the dossier submitter without further comment.

Irritation

The German proposal related specifically to respiratory tract irritation, and the following text is reproduced directly from the appropriate summary and discussion section of the submitted report.

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, the dossier submitter proposed to classify vinyl acetate for respiratory irritation: Xi; R37 (DSD) and STOT SE 3 (H335, may cause respiratory irritation) (CLP).

RAC Opinion

The evaluation by RAC relates to the classification proposal of the dossier submitter, whose proposal was in line with the agreed TC C&L recommendation and was not questioned during public consultation.

For assessment of respiratory irritation, no specific animal tests were available. A retrospective study on 21 operators, that had been exposed at work acutely to high levels of vinyl acetate vapour (>21.6 ppm), revealed local irritant effects in the respiratory tract. In general acute inhalation tests, severe respiratory irritation at 4000 ppm and severe irritation of mucous membrane were seen in rats following 1-10 min exposure to saturated vinyl acetate vapours. In repeat dose toxicity studies, clinical signs of respiratory distress and histopathological changes were further indicative of respiratory irritation observed during and at the end of studies. Based on a comparison of these data with the relevant classification criteria, RAC agrees that these data fit proposed classification of Xi; R37 (DSD) and STOT SE 3; H335 (CLP). RAC accepted this proposal of the dossier submitter without further comments.

Carcinogenicity

The dossier submitted by Germany included a detailed analysis of all the available data relating to the carcinogenicity of vinyl acetate, including that on repeated dose toxicity and mutagenicity. These data have previously been considered in detail under the framework of the Existing Substances Regulation and a definitive view on the carcinogenicity classification of vinyl acetate has been agreed by TC C&L.

Data summary

The following text summarising the data used to support the classification proposal is reproduced directly from the appropriate summary and discussion section of the submitted report.

“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 (Owen, 18, Bogdanffy et al., 994b).

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."

A comprehensive discussion on the mode of action for vinyl acetate is included in the EU RAR (2008). The following summary relating to the classification was provided by the Dossier Submitter.

"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."

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].

Argument for classification

The Dossier Submitter proposed that vinyl acetate should be classified with Carc. Cat. 3; R40 (DSD), which corresponds to Carc. 2; H351 (CLP). Their argumentation was taken directly from the documents provided previously to TC C&L, who supported the proposal. The following text has been reproduced from that documentation:

"There are no adequate data relating specifically to the carcinogenicity of vinyl acetate on humans.

[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.

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".

In addition, the following summary of mechanistic considerations was agreed by TC C&L.

"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 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."

RAC Opinion

The classification proposal is in line with the agreed TC C&L recommendation. During public consultation (and RAC discussion), no comments were received that questioned the proposal to classify vinyl acetate for carcinogenicity. Consequently, based on an observed increase in rates of several tumour types in rats and mice in target organs, by a proposed mechanism that could be relevant to humans, it is the opinion of RAC that classification of vinyl acetate for carcinogenicity is justified.

In accordance with the criteria in the CLP Regulation, classification in category 1A for carcinogenicity is not appropriate, given that the available human data was not sufficient to evaluate the carcinogenic potential of vinyl acetate. It is therefore necessary to decide whether to classify vinyl acetate in category 1B or category 2.

Since an increase in tumour incidence has been observed in two species and by two routes of exposure, an argument for classification in category 1B could have been proposed. However, on consideration of the available data, there are a number of factors that indicate that classification in category 2 would be more appropriate.

Most significantly, the extensive mechanistic data suggests that vinyl acetate is carcinogenic by a secondary mechanism with a practical threshold. After inhalation and oral exposure, vinyl acetate is rapidly and effectively hydrolysed to acetic acid and acetaldehyde, the latter is then converted to acetic acid by aldehyde dehydrogenase. The similarities of toxic and carcinogenic effects of vinyl acetate to those of acetaldehyde indicated that acetaldehyde is the critical metabolite that is responsible for the carcinogenic activity of vinyl acetate.

Vinyl acetate exhibits local genotoxicity, which again is considered to be caused by the hydrolysis product, acetaldehyde. The effect is thought to have a threshold as the accumulation of acetaldehyde is dependent on the activities of the enzymes involved, i.e. acetaldehyde could accumulate if aldehyde dehydrogenase is saturated

The 'Guidance on the application of the CLP Criteria' states that the existence of a secondary mechanism of action with the implication of a practical threshold above a certain dose level may lead to a classification in category 2 rather than category 1.

A further factor indicating that a category 2 classification is the more appropriate one, is the strongly irritant nature of vinyl acetate (as seen in the inhalation studies), which is likely to limit the prolonged exposure of humans to concentrations above the carcinogenic threshold. Additionally, high doses were required to induce tumours, and they were generally at around the maximal tolerated dose in the experiments conducted.

A further doubt about the relevance of the carcinogenic findings was presented by the observation that although repeated inhalation of vinyl acetate produced an increased tumour incidence in rats, no such increase was seen in mice.

In view of these considerations, RAC follows the proposal of the dossier submitter and the recommendation previously agreed at TC C&L, that based on the available evidence vinyl acetate best fits the criteria for classification as Carc. 2; H351 (CLP) and Carc. Cat. 3; R40 (DSD).

Mutagenicity

The dossier submitter presented the data on vinyl acetate mutagenicity in support of the proposal to classify this substance for carcinogenicity, and to show that no further classification for mutagenicity is warranted. Since this position was agreed by TC C&L, the following information on the mutagenicity of vinyl acetate is a copy from the relevant summary and discussion in the background document.

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 LD_{50} 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.

RAC Opinion

The classification proposal is in line with the agreed TC C&L recommendation. During the public consultation no information opposing this evaluation was received. The dossier submitter concluded that a classification for germ cell mutagenicity is not warranted. RAC accepted this proposal of the dossier submitter and TC C&L without further discussion.

Other Hazard Classes

Flammability

The following information was provided by the dossier submitter.

Vinyl acetate meets the classification criteria for a 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 an 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: F, R11 (DSD), Flam. Liq. 2; H225 (CLP)

RAC Opinion

The classification proposal is in line with the agreed TC C&L recommendation and was not questioned during public consultation.

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.

(CLP: Flash point <23°C, boiling point>35°C, DSD: Flash point<21°C, not extremely flammable (Flash point <0°C, boiling point≤35°C))

Proposed classification: F, R11 (DSD), Flam. Liq. 2; H225 (CLP)

Explosivity: additional classification with EUH019 for non stabilized vinyl acetate

The following information was provided by the dossier submitter.

[Vinyl acetate monomer]...is volatile and tends to self-polymerise, and is therefore stored and handled cool and inhibited, with storage limited to below 6 month.

[It]…is 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 be classified additionally with R19/EUH019.

RAC Opinion

The available data show that vinyl acetate is a highly flammable liquid and can form an explosive mixture with air (2.6 – 13.4 vol %). It is known to be stable in contact with air at room temperature for prolonged periods of time (days), and there are no chemical groups present in the molecule associated with explosive properties. Regarding oxidising properties, the substance contains oxygen which is chemically bonded only to carbon or hydrogen.

Vinyl acetate monomer (VAM) may be subject to rapid spontaneous polymerisation if it is not supplied with an appropriate inhibitor or if that inhibitor becomes depleted during prolonged storage. Spontaneous polymerisation is especially likely if cross contamination occurs. The stability of VAM is finite and depends on the concentration of inhibitor present, the temperature of the storage vessel and other conditions. To avoid polymerisation, it is necessary to ensure that cross contamination does not occur, that the temperature is not increasing, and that the inhibitor concentration does not decrease below an effective level.

Vinyl acetate can be stored and transported in containers of steel, aluminium and stainless steel. Non-stabilised vinyl acetate should be kept cool and overlayed with nitrogen to avoid polymerisation.

There is no information in the dossier submitter's proposal about the effective level of inhibitor for different times of storage.

Currently, the harmonised classification of vinyl acetate (Annex VI, CLP) makes direct provision for stabilised vinyl acetate, and indirect provision for the non-stabilised form by inclusion of Note D. However, the dossier submitter proposed creating two entries, creating different harmonised classifications for the stabilised and non-stabilised forms, respectively. This would simply result in an additional labelling for non-stabilised vinyl acetate with R19/EUH019 (May form explosive peroxides), whereas the stabilised form would remain classified as before without R19/EUH019. Presumably, if there were to be two entries, Note D would no longer be required.

The public consultation has indicated that two Competent Authorities could in principle support the creation of a new entry specifically for the non-stabilised form of vinyl acetate, which would include labelling with R19/EUH019. However, industry would be opposed to such additional labelling. Industry provided the following reasoning:
(i) According to experimental investigations, vinyl acetate polyperoxide is not sufficiently stable to increase to a concentration level that forms explosive peroxides.

(ii) Peroxides may act as initiator of an autopolymerisation reaction, but are consumed in this process and do not build up explosive concentration levels.
Further details in support of the industry position are given in the Table of Comments (Annex 2).

According to the classification criteria in the DSD, Annex VI, 2.2.6 and in the CLP Regulation, Annex II, 1.1.5: R19/EUH019 "May form explosive peroxides" shall be assigned to the substances and preparations which may form explosive peroxides during the storage, e.g. diethyl ether, 1,4-dioxan." Consequently, R19/EUH019 indicates that peroxides are formed and that those peroxides are explosive.

RAC noted that no justification was provided by the dossier submitter for the addition of two entries or for the addition of R19/EUH019, which relates to a non-harmonised endpoint. The reasoning for this proposal was simply given by a citation from the well-known Bretheric's Handbook of Reactive Chemical Hazards. There was no further information on the properties of peroxides formed and on other sources that would initiate exothermic polymerisation. No data were presented to show that vinyl acetate will form an explosive level of peroxides during storage, and the peroxides formed by auto-oxidation of acetaldehyde are not explosive themselves. Peroxides may act as initiators of an autopolymerisation reaction but are consumed in this process and do not build up to explosive levels.

RAC member comments were in support to keeping one entry for vinyl acetate with Note D, and for not including EUH019/R19. RAC is of the opinion that this is, as currently, adequate to cover the potential for this substance to be supplied in a stabilised or non-stabilised form. However, this position doesn't exclude the possibility for the supplier to label non-stabilised form of vinyl acetate with EUH019/R19.

Finally, RAC believes that the storage conditions of a particular container of vinyl acetate should be reflected by the supplier in the precautionary statements applied to the labelling. Although it will not have the same regulatory impact as it is not harmonised, the use of specific precautionary statements related to peroxide formation and spontaneous polymerisation can be applied by the supplier to the labelling (e.g. P233 (Keep container tightly closed), P234 (Keep only in original container), P235 (Keep cool), P280 (Wear protective gloves/protective clothing/eye protection/face protection)). However, it is recognised that there is no provision in CLP Annex VI for this to be indicated formally.

Additional information

The Background Document, attached as Annex 1, gives the detailed scientific grounds for the Opinion.

ANNEXES:

Annex 1 Background Document (BD)[2]

Annex 2 Comments received on the CLH report, response to comments provided by the dossier submitter and rapporteurs' comments (excl. confidential information)

[2] The Background Document (BD) supporting the opinion contains scientific justifications for the CLH proposal. The BD is based on the CLH report prepared by a dossier submitter. The original CLH report may need to be changed as a result of the comments and contributions received during the public consultation(s) and the comments by and discussions in the Committees.