Recommendation from the Scientific Committee on

Occupational Exposure Limits

for Vinyl Acetate

8 hour TWA :	5 ppm [17.6 mg/m^3]
STEL (15 mins):	10 ppm [35.2 mg/m^3]
Notation:	-

Substance Identity and Properties:

Vinyl acetate	$CH_3CO\text{-}O\text{-}CH{=}CH_2$
Synonyms:	acetic acid vinyl ester
Chemical Name	acetic acid ethenyl ester
CAS Number:	108-05-4
EINECS Number:	203-545-4
Molecular Weight:	86.09
Melting point:	-93.2°C
Boiling point:	72.3°C at 760 torr
Vapour pressure:	115 torr at 25°C
EU-Classification:	F; R11 Highly flammable.
Conversion at 25°C:	1 ppm = 3.52 mg/m^3; 1 mg/m^3 = 0.28 ppm

Occurrence and Use:

Vinyl acetate is a colourless, volatile and inflammable liquid with an odour described as either sweet and "ether-like", or sharp and sour. It usually contains an inhibitor, hydroquinone, for storage of the chemical. Odour thresholds are reported between 0.36 and 0.5 ppm. Vinyl acetate polymerises when exposed to light.

Vinyl acetate is not known to occur naturally. It is used to produce polyvinyl acetate emulsions and polyvinyl alcohol. The principle use of the polymers is in adhesives, paints, textiles, and paper products. Copolymers have been used in vinyl floor tiles and phonograph records (ACGIH 1992).

Health Significance:

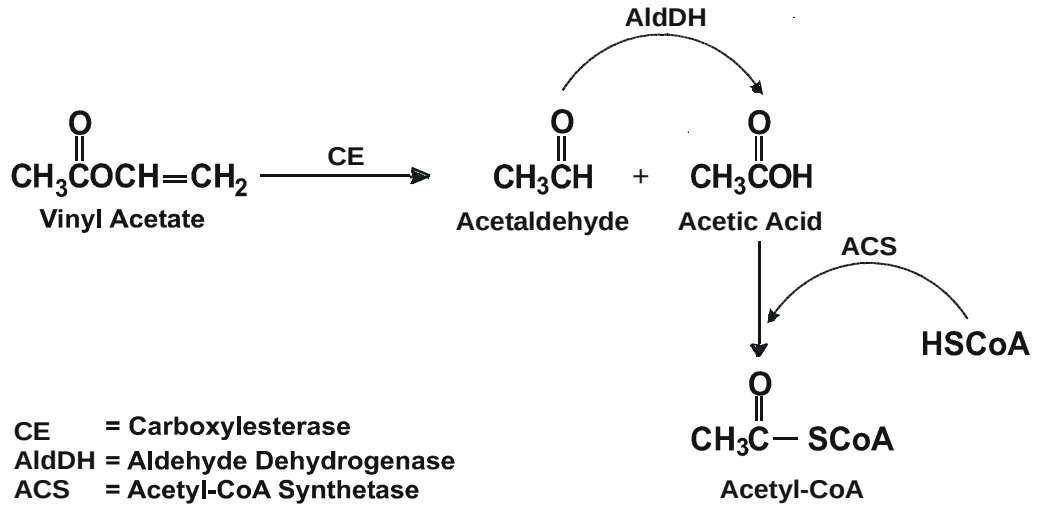
Vinyl acetate is of low acute toxicity after ingestion and dermal absorption, while inhalation of higher concentrations is acutely irritating and toxic. Prolonged exposure to the substance may have irritative or caustic effects to the skin and irritative effects to the eye. According to ACGIH (1992), a NOAEL (no observed adverse effect level) for sensory irritation of the respiratory tract in man is 10 ppm.

In rats LD_{50} values were in two studies 3470 mg/kg and 3500 mg/kg, respectively. A dermal LD_{50} value of 7440 mg/kg was determined from a range finding study with rabbits. Vinyl acetate has proven to cause irritation or corrosion to the skin of rabbits depending on the duration of the skin contact. Exposed workers are principally exhibiting local irritant reactions of the skin, eyes and respiratory tract (information by the vinyl acetate industry, without further details). There is no conclusive information available on skin sensitization in humans. No cases of sensitization from the handling of vinyl acetate in the workplace have been reported in the last years. Results from an animal skin sensitization study (Buehler Test) pointed to the possibility of a moderate skin sensitizing potential of vinyl acetate (DFG 2002). However, a subsequent lymph node assay in mice with vinyl acetate was negative (Wang-Fan 2003).

Cell proliferation of the oral mucosa and the respiratory and olfactory epithelia is observed after repeated exposure. With repeated inhalation exposure the NOAEL for local and systemic effects is 50 ppm in the rat and mouse (*v.i.*). Inhalation of vinyl acetate concentrations of 1000 ppm was maternally toxic and foetotoxic in Sprague-Dawley rats. Oral administration of 5000 mg/l drinking water caused maternal toxicity but not prenatal toxicity in Sprague-Dawley rats. In a 2-generation study, the fertility of F_0 Sprague-Dawley rats was not impaired at this concentration, while that of the offspring was (DFG 2002).

Toxicokinetics/Metabolism

Fig. 1:
Biotransformation Pathways for Vinyl Acetate
(modified, Bogdanffy et al. 1998, EU Draft Risk Assessment Report 2003)



Vinyl acetate is hydrolysed by carboxylesterases to acetic acid and acetaldehyde which is subsequently oxidized to acetic acid by aldehyde dehydrogenases. Acetate enters the citric cycle in an activated form as acetyl coenzyme A. Vinyl acetate metabolism takes place in a multiplicity of tissues, which is of relevance for the toxicological effects elicited by vinyl acetate. The hydrolytic cleavage of vinyl acetate in the organism is catalysed by ubiquitous esterases (Simon et al. 1985a, Fedtke and Wiegand 1990). Upon inhalation, this occurs within the epithelia of the upper respiratory tract (Robinson et al. 2002). The local irritation and cytotoxicity of vinyl acetate are explained by the intracellular acidity resulting from the metabolically formed acetic acid (Kuykendall and Bogdanffy 1992, Kuykendall et al. 1993), and the threshold level for these effects has been linked with the physiological buffer capacity (Bogdanffy 2002).

The rapid hydrolysis of vinyl acetate is the reason for a basic difference in metabolism and toxicity compared to other vinyl compounds (*e.g.* vinyl chloride, vinyl bromide, vinyl carbamate): vinyl acetate is not epoxidised at the vinyl group to a genotoxic and DNA-binding oxirane metabolite (Simon et al. 1985b, 1986).

The amount of inhaled vinyl acetate absorbed was determined in the upper respiratory tract of anaesthetized rats. The exposure concentrations were 73 to 2190 ppm with inhalation for one hour. After exposure for about 8 minutes, an equilibrium was reached for vinyl acetate in nasal tissue. The concentration-dependent absorption of vinyl acetate by the epithelia was non-linear and between 36 % and 94 %, with the highest percentage absorbed at the lowest vinyl acetate concentrations (at 76 ppm or less, more

than 93 % vinyl acetate was absorbed). At all vinyl acetate concentrations acetaldehyde was detected as a metabolite in the exhaled air (Plowchalk *et al*. 1997).

Species differences between rats and mice are small for the kinetic parameters of the esterases in the nasal epithelium (Bogdanffy and Taylor 1993, Robinson et al. 2002, Morris *et al*. 2002, Bogdanffy and Taylor 1993). In mucosa obtained from the oral cavity of rats and mice, carboxylesterase was ubiquitously present, but with local differences in the activity of the enzyme.

According to a PBPK model for the dosimetry of vinyl acetate and its metabolites acetaldehyde and acetic acid in the nasal cavity, a significant drop in the intracellular pH value in the olfactory epithelium of the rat was stated to occur only above 50 ppm, due to limitation of the intracellular buffer capacity (Bogdanffy *et al*. 1999, 2001, Andersen *et al.* 2002).

Genotoxicity

In prokariotic cell systems *in vitro* (*Salmonella* mutagenicity test, SOS chromotest) no mutagenic potential was found. On incubation with eukariotic cells, however, dose-dependent effects such as chromosomal aberrations, sister chromatid exchange and micronuclei are observed. Evidence of the occurrence of DNA cross-links was obtained after the incubation of very high concentrations of vinyl acetate with human lymphocytes. Under *in vivo* conditions no stable DNA adducts were found. On the other hand, after mice were given single intraperitoneal injections of 1000 or 2000 mg/kg body weight, an increase in the micronucleus count in bone marrow cells was found. In the same experiment no micronuclei were found in the male germ cells (spermatids).

After rats and mice inhaled the substance or were given oral doses in the drinking water for 3 months, no micronuclei were found in the bone marrow (EU Draft Risk Assessment Report 2003).

After the incubation of plasmid DNA, calf thymus histone proteins and rat liver microsomes with 1 to 100 mM vinyl acetate, DNA-protein cross-links were formed as a result of the formation of acetaldehyde. After incubation with acetaldehyde, a reduction in the pH value promoted cross-links (Kuykendall and Bogdanffy 1992). Also in isolated cells of the respiratory and olfactory epithelium of rats, vinyl acetate induced DNA-protein cross-links; their formation could be reduced by the inhibition of the carboxyl esterases *in vivo* and *in vitro*. When equimolar amounts of vinyl acetate and acetaldehyde were used, more cross-links were formed by vinyl acetate. As more acetic acid is formed with vinyl acetate than with acetaldehyde on an equimolar basis, the authors suspect that the greater drop in the pH value of vinyl acetate is responsible. Vinyl acetate was cytotoxic for both epithelia. The aldehyde scavenger semicarbacide could not reduce the cytotoxicity, 50 mM acetaldehyde alone was not cytotoxic, but 50 mM acetic acid was (Kuykendall *et al*. 1993).

In an inadequately documented study it was reported that after single intraperitoneal doses of vinyl acetate of 160 mg/kg body weight, chromosomal aberrations were found in the bone marrow of rats 26 hours after administration of the substance (EU Draft Risk Assessment Report 2003).

Likewise, the incidence of SCE in bone marrow was increased in rats 21 hours after intraperitoneal administration of vinyl acetate doses of 370–560 mg/kg body weight (Takeshita *et al*. 1986).

Comparative *in vitro* studies with acetaldehyde indicate that the genotoxic effects of vinyl acetate are to be attributed to the metabolite acetaldehyde (He and Lambert 1985, Norppa *et al*. 1985).

The overall picture obtained from studies of the genotoxicity of vinyl acetate *in vivo* is that systemic genotoxic effects after ingestion or inhalation were not detected. After high intraperitoneal doses resulting in death, however, an increase in micronuclei in bone marrow cells was observed; this is explained by the saturation of inactivation mechanisms. At high doses, mutagenic effects of vinyl acetate (induced by the metabolite acetaldehyde) on tissues directly exposed locally cannot be excluded.

With regard to the metabolic formation of acetaldehyde, the detoxification capacity of the organism, as well as the endogenous presence of ethanol and acetaldehyde must be borne in mind. The endogenous level of acetaldehyde in the blood is given in the literature as 0.3 mg/ml (Halvorson *et al*. 1993).

Drinking water studies

The half-life of vinyl acetate in aqueous solution (distilled water) is about one week (Bogdanffy *et al*. 1994a). This is important when evaluating some of the studies with oral administration.
In a 13-week study with F344 rats and BDF_1 mice, no treatment-related histopathological changes were reported. The vinyl acetate concentrations in drinking water were 600, 1500, 3800, 10000 or 24000 mg/l (assuming water consumption to be 10 % in rats and 15 % in mice, this corresponds with a daily consumption of 2400 mg/kg body weight in rats and 3600 mg/kg body weight in mice; no other details; Ministry of Labour of Japan 1998).

Groups of 20 male F344 rats (CDF) and BDF_1 mice (BGD2F1/CrlBr) were given drinking water containing vinyl acetate in concentrations of 1000, 5000, 10000 or 24000 mg/l for 90 days. The highest concentration was limited by the solubility. This study was designed in particular to determine threshold concentrations for local cell proliferation processes. Based on the drinking water consumption, the daily doses for rats were calculated to be 81, 350, 660 and 1400 mg/kg body weight and for mice 250, 1200, 2300 and 5300 mg/kg body weight. Statistically significant reductions in food consumption were observed in the rats exposed to 10000 and 24000 mg/l. There was a statistically significant reduction in the body weights of the rats of all groups. In mice, no effects on water and food consumption, or body weight gains were detected. No treatment-related histopathological changes were found in the oral cavity, oesophagus or for estomach of the animals. In rats, increased proliferation was found at concentrations of 24000 mg/l in the mucosa (BrdU incorporation; but below a doubling of the labelling index) in the lower jaw on days 1 and 29 (but not on day 8) and in the upper jaw on days 29 and 92. In the mice, increases in cell proliferation of 2.4 and 3.4 times those found in the controls occurred only after 92 days in the mucosa of the lower jaw following concentrations of 10000 and 24000 mg/l (Valentine *et al*. 2002).

A 78-week study with Swiss mice with vinyl acetate concentrations of 1000 or 5000 mg/l drinking water yielded a NOAEL for systemic effects of 5000 mg/l drinking water (750 mg/kg body weight and day; Maltoni *et al*. 1997).

Groups of 60 Sprague-Dawley rats per sex and dose were given vinyl acetate with the drinking water in concentrations of 200, 1000 or 5000 mg/l (males: 10, 47 and 202 mg/kg body weight and day; females: 16, 76 and 302 mg/kg body weight and day), beginning *in utero*, for a period of 2 years. The solutions were freshly prepared each day. The clinical symptoms, body weights, food and water consumption, haematology, clinical chemistry, urine composition, and gross pathological and microscopic changes were determined. Rats of the 1000 and 5000 mg/l groups consumed less water. In the 5000 mg/l groups, food consumption and body weights were reduced (males: –19 %; females: –11 %). No treatment-related changes in mortality, in the haematological and clinico-chemical parameters or the urine status were observed. There was also no evidence of systemic organ toxicity. Some organ weights were changed in the 1000 and 5000 mg/l groups; no histopathological changes were found, however, and the changes were attributed to the lower body weights. The NOAEL was 1000 mg/l (Bogdanffy *et al*. 1994a).

New-born Wistar rats (4–5 animals per sex) were given oral doses of vinyl acetate in condensed milk of 100 or 200 mg/kg body weight and day (99 % pure, impurities: 100 mg hydroquinone/l) twice a day over a period of 3 weeks. A subgroup of animals was additionally treated with phenobarbital in drinking water for 8 weeks to stimulate the growth of potential preneoplastic liver foci. 14 weeks after the beginning of the study the animals were killed and their livers examined. No ATPase-free and gamma-GT positive areas could be found in the liver as evidence of the development of preneoplastic liver foci (Laib and Bolt 1986).

There are several additional studies available of the effects of vinyl acetate after ingestion, but the quality of some is considerably lacking.

A long-term study with oral has been published (Bogdanffy *et al*. 1994a). Groups of 60 Sprague-Dawley rats (per sex and dose) were given vinyl acetate with the drinking water in concentrations of 200, 1000 or 5000 mg/l (males: 10, 47 and 202 mg/kg body weight and day; females: 16, 76 and 302 mg/kg body weight and day), beginning *in utero*, for a period of 2 years. In the male rats of the highest dose group, 2 squamous cell carcinomas of the oral cavity were found and a sarcoma in the stomach. The tumour incidence for oral cavity carcinomas was, however, within the range of the historical control data for the strain and age of the rats used (Bogdanffy *et al*. 1994a).

Groups of 50 male and 50 female F344 rats and BDF_1 mice were given vinyl acetate with the drinking water in doses of 400, 2000 or 10000 mg/l for a period of 104 weeks (rats, males: 16–48, 75–226 and 364–950 mg/kg body weight and day; females: 22–60, 109–266 and 478–1062 mg/kg body weight and day, mice, males: 32–85, 167–405 and 800–2081 mg/kg body weight and day, females: 45–125, 230–483 and 1024–2185 mg/kg body weight and day). The vinyl acetate solutions were prepared twice a week. After the end of exposure the animals were killed and the weights of the brain, lungs, liver, spleen, heart, kidneys, adrenal glands, testes and ovaries were determined. The histopathological examinations in all animals covered 37 organs and tissues including the nasal cavity. In rats the increased tumour incidences in the oral cavity, the oesophagus and the stomach were regarded as treatment-related. In the oral cavity a

positive trend was found for the incidence of squamous cell carcinomas in female animals. The increase was statistically significant in the male animals of the 10000 mg/l group. At this concentration squamous cell papillomas were observed in 2/50 male animals, epithelial dysplasia in 2/50 female animals and squamous cell carcinomas of the oesophagus in 1/50 female animals. Preneoplastic lesions of the oesophagus and the stomach were evident only at this concentration. No stomach tumours were found. In mice, exposure-related tumours were found in the oral cavity, oesophagus, stomach and larynx. Particularly after doses of 10000 mg/l (depending on the organ), statistically significant squamous cell carcinomas, papillomas and hyperplasia, basal cell activation and epithelial dysplasia developed. The highest concentration was, however, above the maximum tolerated dose, as the body weight curves show a reduction in body weight gains of at least 10 %. The nominal vinyl acetate concentration was not analytically verified, however, nor was drinking water consumption determined (Umeda et al. 2004).

Another long-term study consisted of the summary of a study carried out very much earlier against the background of studies for vinyl chloride. In this study Swiss mice were given vinyl acetate with the drinking water in doses of 1000 or 5000 mg/l for a period of 78 weeks. The F_0 generation (13–14 male and 37 female animals/group) and their young (37–38 male and 44–48 female animals/group) were treated from day 12 of gestation. The animals were observed up to the natural end of their lives. The drinking water was freshly prepared each day. No treatment-related effects were found as regards survival, body weight and behaviour. An increased tumour incidence was found in the following organs: Zymbal gland, oral cavity, tongue, oesophagus, for estomach, lungs, liver and uterus (Maltoni et al. 1997). Interpretation of these results is difficult when the large number of spontaneous systemic tumours in the control animals of this study is taken into consideration. The study appears compromised because of the following reasons: mortality was also high in untreated animals in the second year of the experiment. The nominal vinyl acetate concentrations and the drinking water consumption were not monitored. The maximum tolerated dose was probably exceeded in the F_1 animals, as body weight gains were reduced by at least 10 % at the highest dose (at which the tumours were reported). However, as the oral cavity, tongue, oesophagus and for estomach are locations coinciding with those in the results obtained by Umeda et al. (2004), this study is supportive of the latter study.

Inhalation studies

In a long-term study, vinyl acetate caused local tumours in the rat after inhalation of a markedly irritative concentration and in the rat and mouse after oral administration of concentrations which were not cytotoxic, but already of systemic toxicity.

To investigate the effects on cell proliferation in the olfactory and respiratory epithelia of the nasal cavity, rats were exposed to vinyl acetate once or repeatedly for up to 4 weeks (50, 200, 600 or 1000 ppm; 6 hours/day). The NOAEL for all effects was 200 ppm. With higher concentrations and single exposures cell proliferation was markedly increased. With exposure for 5 days, the NOAEL was 1000 ppm, with exposure for 20 days 200 ppm (olfactory epithelium only). After exposure to concentrations of 600 ppm or more for 4 weeks, regenerative hyperplasia was observed in the olfactory epithelium, and necrosis at 1000 ppm (Bogdanffy *et al*. 1997).

In a 10-month study with Wistar rats exposed to vinyl acetate concentrations of 2.8, 28 and 140 ppm (5 hours/day, 5 days/week), metaplasia of the bronchial epithelium was found in all treated animals. The medium and high concentration caused, in addition,

liver changes in the form of fatty degeneration of the liver and proliferation of the endoplasmic reticulum, and histological changes in the biliary capillaries (Czajkowska *et al*. 1986). The results of this study are in contradiction to those found in the much better documented study of Bogdanffy *et al*. (1994b) and are therefore not included in the evaluation of vinyl acetate.
One inhalation study with rats with negative results (Maltoni *et al*. 1974) is only very inadequately documented, the exposure period of 52 weeks does not meet present-day standards and mortality was very high; therefore, no conclusions can be drawn from this study.
In a 2-year study (Bogdanffy *et al.* 1994b) Sprague-Dawley rats and CD-1 mice were exposed to vinyl acetate in concentrations of 50, 200 or 600 ppm over a period of 2 years (6 hours/day, 5 days/week). At concentrations of 600 ppm reduced urine volumes were determined in the rats. This was attributed to reduced food and water consumption, but no data were collected for this. Reduced body weights were determined in mice after concentrations of 200 ppm or more and in rats after 600 ppm. Vinyl acetate affected only the upper and lower respiratory tract (*see Appendix: Table 1, rats, and Table 2, mice*). After concentrations of 200 ppm or more, atrophy, regenerative processes, inflammation and metaplasia in the olfactory epithelium, and basal cell hyperplasia were found in rats and mice. Hyperplastic and metaplastic changes in the trachea, together with epithelial desquamation and fibrotic reactions of the tracheal epithelium were observed only in mice at 600 ppm. Similar changes were found in the bronchial and bronchiolar airways of rats and mice at 600 ppm. In addition, histiocytic cell accumulation in the alveoli and the pulmonary interstitium was observed, which is possibly connected with the increased lung weights (Bogdanffy *et al*. 1994b). The following NOAELs were obtained: local effects: 50 ppm in rats and mice; systemic effects (end point reduced body weights): 200 ppm in rats, 50 ppm in mice (EU Draft Risk Assessment Report 2003). *Table 3* (*Appendix*) shows the tumour incidences observed in this study. This study revealed local carcinogenic effects after inhalation exposure of the rat to markedly irritative concentrations (*compare with Table 1*). In the olfactory epithelium 3 papillomas and 2 carcinomas were found, in the respiratory epithelium 2 inverted papillomas. Five other carcinomas were found at other sites or were of unknown origin (no other details). In mice no tumours were found, but irritation of the nasal epithelia was observed (*see Appendix, Table 2*; Bogdanffy *et al*. 1994b).

Evaluation of carcinogenicity and mode of action

In two epidemiological studies with exposure to a mixture of substances, no statistically valid evidence of carcinogenic effects of vinyl acetate in man was found. No differentiation was made between persons exposed to high levels and those to low levels, and the influence of smoking habits was not excluded. The data are therefore not considered meaningful (DFG 2002).
The biological mode of action of vinyl acetate is linked with its rapid metabolism by ubiquitous esterases by which acetaldehyde and acetic acid are formed.
In 2-year drinking water studies with F344 rats and BDF_1 mice, tumours of the oesophagus and oral cavity (rats, mice) and stomach and larynx (mice) were induced at the highest concentration of 10000 mg/l. This shows that local tumours can be induced with high oral exposure to vinyl acetate in the drinking water. An inhalation carcinogenicity study with rats and mice yielded local tumours of the nasal mucosa of the rat at 600 ppm, while in the mouse no tumours were observed. Compared to that of acetaldehyde, the potential of vinyl acetate to produce tumours of the nasal mucosal

epithelium of the rat is evidently smaller, as in the long-term inhalation study (28 months) with acetaldehyde at 750 ppm the incidence of adenocarcinomas of the nasal cavity (Woutersen *et al*. 1986) was much greater than in the long-term study (24 months) with vinyl acetate at 600 ppm. On the other hand, the irritative effects of vinyl acetate are greater than those of acetaldehyde.

Vinyl acetate causes DNA–protein cross-links *in vitro*. This effect is attributed to the metabolite (hydrolysis product) acetaldehyde. In the *Salmonella* mutagenicity test, the substance is not mutagenic. Vinyl acetate produces positive results in the micronucleus test, the chromosomal aberration test and SCE (sister chromatid exchange) test *in vitro*. *In vivo*, after very high single intraperitoneal doses, micronuclei and SCE were observed in the bone marrow cells of mice, but not after inhalation exposure or the administration of vinyl acetate in drinking water. A micronucleus test *in vivo* in germ cells (spermatids) yielded negative results (EU Draft Risk Assessment Report 2003).

The findings in studies of the carcinogenicity of vinyl acetate may be explained by the local cytotoxicity resulting from the local metabolism to acetaldehyde and acetic acid on the one hand, and by the local genotoxic effects of its metabolite acetaldehyde on the other hand (Bogdanffy and Valentine 2003). The concept has been put forward that the carcinogenic effects of vinyl acetate are subject to a threshold, below which no notable contribution towards the cancer risk in man is to be expected (Lantz and Bogdanffy 2003). This is supported by a non-linear course of the dose–effect relationships in the carcinogenicity studies (Hengstler et al. 2003).

A physiologically-based pharmacokinetic model has been generated to describe the local metabolism and effects of vinyl acetate at the nasal tissue (Bogdanffy et al. 1999, 2001, Andersen et al. 2002). This model has been criticised (DFG 2002), and supplementary data on the application were subsequently generated (Hinderliter et al. 2005), along with studies of the histochemical localisation of the carboxyesterase activity in rat and mouse oral cavity tissues (Robinson et al. 2002) and on pH effects in rat nasal epithelial tissue explants and in cultured respiratory and olfactory epithelial cells (Lantz et al. 2003). Also, it has been demonstrated that vinyl acetate induces intracellular acidification in isolated mouse oral buccal epithelial cells (Nakamoto et al. 2005). In essence, these studies supported the view that carboxyesterase was active at the sites of local experimental tumour formation. Also, the data obtained with cultured nasal epithelial cells and tissue explants supported a relevant decrease in intracellular pH upon presence of vinyl acetate.

Conclusions and recommendations

Vinyl acetate was found to have genotoxic effects *in vitro*, e.g. chromosomal aberrations, micronuclei and SCE, and gene mutations were observed in mammalian cell cultures. *In vivo*, after very high single intraperitoneal doses, micronuclei were observed in the bone marrow cells of mice, but not after inhalation exposure or the administration of vinyl acetate in drinking water. A micronucleus test in germ cells (spermatids) yielded negative results. The substance is therefore not to be regarded as a germ cell mutagen under conditions of workplace exposure.

Two-year inhalation experiments in mice and rats have proven a concentration of 50 ppm (ppm) to be a NOAEL, with respect to local histopathological changes of nose and lungs (*see Appendix: Tables 1 and 2*). Also, the systemic NOAEL (reduced body weights in mice) from the inhalation carcinogenicity study is 50 ppm (175 mg/m^3). This confirms early industrial information on concentrations up to 10 ppm being unlikely to produce respiratory or ocular irritation in most workers, whereas concentrations above

20 ppm appeared to produce irritation in the majority of exposed workers (ACGIH 1992). The American Conference of Governmental Industrial Hygienists had based its recommendation of a Threshold Limit Value (8h TWA: 10 ppm, STEL: 20 ppm) on this information, in order to avoid irritancy (ACGIH 2002).
In essence, vinyl acetate is carcinogenic at portals of entry (nasal cavity and upper gastrointestinal tract). Local metabolism of vinyl acetate produces the DNA-reactive and genotoxic acetaldehyde, and it also produces acetic acid, contributing to intracellular acidification, cytotoxicity and cell proliferation. Elevated cellular proliferation is observed at concentrations associated with the experimental tumour formation. Cytotoxicity and compensatory tissue regeneration appears as stimulating cellular proliferation while intracellular acidification is a mitogenic stimulus. A physiologically-based pharmacokinetic model is consistent with the concept that intracellular acidification is the sentinel response that precedes cytotoxicity and cellular proliferation. In conclusion, the carcinogenic potential of vinyl acetate is expressed only when tissue exposure to acetaldehyde is high and when cellular proliferation is simultaneously elevated. This mode of action suggests that exposure levels that do not increase intracellular acidification beyond homeostatic bounds will be adequately protective of adverse downstream responses including cancer. This provides the scientific basis to incorporate thresholds for cell proliferation secondary to intracellular acidification. As long as the physiological buffering systems are fully operative, no local carcinogenic effect by vinyl acetate should be expected.
Under these considerations of modes of action, a cancer risk at low, non-irritant, concentrations of vinyl acetate in the workplace air appears negligible. The NOAEL for histological changes in respiratory rodent tissues was 50 ppm. A threshold for sensory irritation may be expected to be lower. There are limited observations in humans (ACGIH 1992) of an NOAEL for irritancy at 10 ppm. Considering these experimental and human data on irritancy and the experimentally observed local carcinogenicity at higher concentrations, a STEL is set at 10 ppm, and an OEL (8h-TWA) at half of this value. Therefore, the following Occupational Exposure Limits are recommended:

OEL (8h-TWA): 5 ppm,
STEL: 10 ppm.

The volatility of the substance and the irritation effects are pronounced and dermal exposure appears less relevant under industrial conditions compared to inhalation exposure (DFG 2002). A “skin” notation is therefore not required.
There is no information available for possible sensitizing effects of vinyl acetate in man. The results of a Bühler test cannot be evaluated, as the possibility of false positive reactions cannot be excluded. A local lymph node assay in mice was negative, so that it appears unlikely that vinyl acetate could be a contact allergen. There are no data available for the sensitizing effects on the respiratory tract.

References

ACGIH (1992) Vinyl acetate. In: Documentation of Threshold Limit Values and Biological Exposure Indices, 6th Edition. American Conference of Governmental Industrial Hygienists, Cincinnatti, OH.
Andersen ME, Green T, Frederick CB, Bogdanffy MS (2002) Physiologically based pharmacokinetic (PBPK) models for nasal tissue dosimetry of organic esters: assessing

the state-of-the-knowledge and risk assessment applications with methyl methacrylate and vinyl acetate. Regulatory *Toxicol Pharmacol 36:* 234-245
Bogdanffy MS (2002) Vinyl acetate induced intracellular acidification: implications for risk assessment. *Toxicol Sci 66*: 320–326
Bogdanffy MS, Valentine R (2003) Differentiating between local cytotoxicity, mitogenesis, and genotoxicity in carcinogen risk assessments: the case of vinyl acetate. *Toxicol Lett 140-141:* 83-98
Bogdanffy MS, Taylor ML (1993) Kinetics of nasal carboxylesterase-mediated metabolism of vinyl acetate. *Drug Metabol Dispos 21*: 1107–1111
Bogdanffy MS, Tyler TR, Vinegar MB, Rickard RW, Carpanini FMB, Cascieri TC (1994a) Chronic toxicity and oncogenicity study with vinyl acetate in the rat: *in utero* exposure in drinking water. *Fundam Appl Toxicol 23*: 206–214
Bogdanffy MS, Dreef-van der Meulen HC, Beems RB, Ferron VJ, Cascieri TC, Tyler TR, Vinegar MB, Rickard RW (1994b) Chronic toxicity and oncogenicity inhalation study with vinyl acetate in the rat and mouse. *Fundam Appl Toxicol 23*: 215–229
Bogdanffy MS, Gladnick NL, Kegelman T, Frame SR (1997) Four-week inhalation cell proliferation study of the effects of vinyl acetate on rat nasal epithelium. *Inhalat Toxicol 9*: 331–350
Bogdanffy MS, Sarangapani R, Plowchalk DR, Jarabek A, Andersen ME (1999) A biologically based risk assessment for vinylacetate-induced cancer and noncancer toxicity. *Toxicol Sci 51*: 19–35
Bogdanffy MS, Plowchalk DR, Sarangapani R, Starr TB, Andersen ME (2001) Mode of action-based dosimeters for interspecies extrapolation of vinyl acetate inhalation risk. *Inhalat Toxicol 13*: 377–396
Carpenter CP, Smyth HF, Pozzani UC (1949) The assay of acute vapour toxicity, and the grading and interpretation of results on 96 chemical compounds. *J Ind Hyg Toxicol 31*: 343–346
DFG (2002) Vinyl Acetat, Nachtrag 2002. In: Deutsche Forschungsgemeinschaft, Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten. 35. Lieferung. VCH Publishers, Weinheim
EU Draft Risk Assessment Report "Vinyl Acetate" (2003) European Chemicals Bureau, Ispra
Fedtke N, Wiegand HJ (1990) Hydrolysis of vinyl acetate in human blood. *Arch Toxicol 64*:428–429
Guy RH, Potts RO (1993) Penetration of industrial chemicals across the skin: a predictive model. *Am J Ind Med 23*: 711–719
Halvorson MR, Noffsinger JK, Peterson CM (1993) Studies of whole blood-associated acetaldehyde levels in teetotalers. *Alcohol 10*: 409–413
He SM, Lambert B (1985) Induction and persistence of SCE-inducing damage in human lymphocytes exposed to vinyl acetate and acetaldehyde *in vitro*. *Mutat Res 158*: 201–208
Hengstler JG, Bogdanffy MS, Bolt HM, Oesch F (2003) Challenging dogma: thresholds for genotoxic carcinogens? The case of vinyl acetate. *Annu Rev Pharmacol Toxicol 43:* 485-520
Hinderliter PM, Thrall KD, Corley RA, Bloemen LJ, Bogdanffy MS (2005) Validation of human physiologically-based pharmacokinetic midel for vinyl acetate against human nasal dosimetry data. *Toxicol Sci 85*: 460-467
Korte A, Obe G, Ingwersen I, Rueckert G (1981) Influence of chronic ethanol uptake and acute acetaldehyde treatment on the chromosomes of bone-marrow cells and peripheral lymphocytes of Chinese hamsters. *Mutat Res 88*: 389

Kuykendall JR, Bogdanffy MS (1992) Reaction kinetics of DNA-histone crosslinking by vinyl acetate and acetaldehyde. *Carcinogenesis 13*: 2095–2100
Kuykendall JR, Taylor ML, Bogdanffy MS (1993) Cytotoxicity and DNA-protein crosslink formation in rat nasal tissues exposed to vinyl acetate are carboxylesterase-mediated. *Toxicol Appl Pharmacol 123*: 283–292
Laib RJ, Bolt HM (1986) Vinyl acetate, a structural analog of vinyl carbamate, fails to induce enzyme-altered foci in rat liver. *Carcinogenesis 7*: 841–843
Lambert B, Chen Y, He SM, Sten M (1985) DNA cross-links in human leucocytes treated with vinyl acetate and acetaldehyde *in vitro*. *Mutat Res 146*: 301–303
Lantz RC, Orozco J, Bogdanffy MS (2003) Vinyl acetate decreases intracellular pH in rat nasal epithelial cells. *Toxicol Sci 75:* 423-431
Maltoni C, Ciliberti A, Lefemine G, Soffritti M (1997) Results of a long-term experimental study on the carcinogenicity of vinyl acetate monomer in mice. *Ann NY Acad Sci 837*: 209–238
Ministry of Labour of Japan (1998) *Toxicology and carcinogenesis studies of vinyl acetate in F 344/DuCr Rats and Crj:BDF$_1$ Mice (drinking water study)*, unpublished
Morita T, Takeda K, Okumura K (1990) Evaluation of clastogenicity of formic acid, acetic acid and lactic acid on cultured mammalian cells. *Mutat Res 240*: 195–202
Morita T, Asano N, Awogi T, Sasaki YF, Sato S-I, Shimada H, Sutou S, Suzuki T, Wakata A, Sofuni T, Hayashi M (1997) Evaluation of the rodent micronucleus assay in the screening of IARC carcinogens (Group 1, 2A and 2B). The summary report of the 6th collaborative study by CSGMT/JEMS MMS. *Mutat Res 389*: 3–122
Morris JB, Symanowicz P, Sarangapani R (2002) Regional distribution and kinetics of vinyl acetate hydrolysis in the oral cavity of the rat and mouse. *Toxicol Lett 126*: 31–99
Nakamoto T, Wagner M, Melvin JE, Bogdanffy MS (2005) Vinyl acetate induces intracellular acidification in mouse oral buccal epithelial cells. *Toxicol Lett* 158: 116-121
Norppa H, Tursi F, Pfäffli P, Mäki-Paakkanen J, Järventaus H (1985) Chromosome damage induced by vinyl acetate through *in vitro* formation of acetaldehyde in human lymphocytes and Chinese hamster ovary cells. *Cancer Res 45*: 4816–4821
Ott MG, Teta MJ, Greenberg HL (1989) Lymphatic and hematopoietic tissue cancer in a chemical manufacturing environment. *Am J Ind Med 16*: 631–643
Plowchalk DR, Andersen ME, Bogdanffy MS (1997) Physiologically based modelling of vinyl acetate uptake, metabolism, and intracellular pH changes in the rat nasal cavity. *Toxicol Appl Pharmacol 142*: 386–400
Ristow H, Obe G (1975) Acetaldehyde induces cross-links in DNA and causes sister-chromatid exchanges in human cells. *Mutat Res 58*: 115–119
Robinson DA, Bogdanffy MS, Reed CJ (2002) Histochemical localisation of carboxylesterase activity in rat and mouse oral cavity mucosa. *Toxicology 180:* 209-220.
Simon P, Filser JG, Bolt HM. (1985a) Metabolism and pharmacokinetics of vinyl acetate. *Arch Toxicol 57:* 191-195
Simon P, Ottenwälder H, Bolt HM (1985b) Vinyl acetate: DNA-binding assay in vivo. *Toxicol Lett 27:* 115-120
Simon P, Epe B, Mützel P, Schiffmann D, Wild D, Ottenwälder H, Fedtke N, Bolt HM, Henschler D (1986) Synthesis and genotoxicity of acetoxyoxirane, the epoxide of vinyl acetate. *J Biochem Toxicol 1:* 43-56
Takeshita T, Iijama S, Higurashi M (1986) Vinyl-acetate induced sister chromatid exchanges in murine bone marrow cells. *Proc Jpn Acad 62*: 239–242
Union Carbide (1969) *Vinyl acetate, range finding toxicity studies*, Report 32–99, unpublished

Umeda Y, Matsumoto M, Yamazaki K, Ohnishi M, Arito H, Nagano K, Yamamoto S, Matsushima T (2004) Carcinogenicity and chronic toxicity in mice and rats administered vinyl acetate monomer in drinking water. *J Occup Health 46*: 87-99
Valentine R, Bamberger JR, Szostek B, Frame SR, Hansen JF, Bogdanffy MS (2002) Time- and concentration-dependent increases in cell proliferation in rats and mice administered vinyl acetate in drinking water. *Toxicol Sci 67*: 190–197
Vinyl Acetate Toxicology Group (1995) *Delayed contact hypersensitivity study in guinea pigs (Buehler technique) of: vinyl acetate*, Hill Top Biolabs Inc, Cincinnati, OH, USA, report No. 94-8486-21, unpublished
Wang-Fan W (2003) *Vinyl acetate (CAS 108-05-4): Local Lymph Node Assay in mice (identification of contact allergens).* RCC Study Number 846925. RCC Ltd., CH-4452 Iltingen
Waxweiler RJ, Smith AH, Falk H, Tyroler HA (1981) Excess lung cancer risk in a synthetic chemicals plant. *Environ Health Perspect 41*: 159–165
WHO (World Health Organization) (1995) *Acetaldehyde*. IPCS – Environmental health criteria 167, WHO, Genf
Woutersen RA, Appelman LM, Van Garderen-Hoetmer A, Feron VJ (1986) Inhalation toxicity of acetaldehyde in rats. III. Carcinogenicity study. *Toxicology 41*: 213–231

Criteria Documents used:

ACGIH (1992)
DFG (2002)
EU Draft Risk Assessment Report (2003)

Appendix: Tables 1-3

Table 1 : Summary of statistically significant non-neoplastic changes in lungs and nose in rats: main study

(EU Draft Risk Assessment Report, 2003)

	Incidence of Lesions Other than Tumors [a]							
	Males				Females			
Concentration (ppm):	Control	50	200	600	Control	50	200	600
Lungs:	(58)	(59)	(60)	(60)	(60)	(60)	(60)	(59)
Bronchial exfoliation								
very slight	0	0	0	8**	0	0	0	0
slight	0	0	0	26**	0	0	0	4
moderate	0	0	0	2	0	0	0	0
Intraluminal fibrous projections								
very slight	0	0	0	16 ***	0	0	0	3
slight	0	0	0	14 ***	0	0	0	28 ***
moderate	0	0	0	1	0	0	0	8 **
severe	0	0	0	0	0	0	0	1
Pigment macrophage								
very slight	1	0	0	0	0	0	0	1
slight	1	3	3	33 ***	6	4	1	10
moderate	0	0	1	2	0	0	0	4
Peribronchiolar/perivascular lymphoid aggregates								
very slight	5	1	0 *	0 *	0	1	2	0
slight	15	18	21	14	11	14	14	23 *
moderate	1	4	1	2	2	1	2	5
Nose:	(59)	(60)	(59)	(59)	(60)	(60)	(60)	(59)
Olfactory epithelial atrophy								
very slight	0	1	4	0	0	1	4	0
slight	0	2	47 ***	7 *	0	0	23 ***	18 ***
moderate	0	0	2	33 ***	0	0	0	30 ***
severe	0	0	0	10 **	0	0	0	3
Olfactory epithelial squamous metaplasia								
very slight	0	0	0	2	0	0	5	4
slight	0	0	0	12 **	0	0	0	26 ***
moderate	0	0	0	9 **	0	0	0	7**
severe	0	0	0	1	0	0	0	0

[a] Figures in parenthesis present the number of animals from which this tissue was examined microscopically. Significance of differences in a pairwise (Fisher´s) test between each treatment and control incidence is indicated by * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Cited from Bogdanffy et al. (1994b)

Table 1 (continued) : Summary of statistically significant non-neoplastic changes in lungs and nose in rats: main study (EU Draft Risk Assessment Report, 2003)

	Incidence of Lesions Other than Tumors [a]							
	Males				Females			
Concentration (ppm):	Control	50	200	600	Control	50	200	600
Nose:	(59)	(60)	(59)	(59)	(60)	(60)	(60)	(59)
Olfactory epithelial regeneration								
very slight	0	0	3	0	0	0	3	2
slight	0	0	30***	1	0	0	16***	7**
moderate	0	0	2	0	0	0	3	0
Olfactory epithelial inflammatory cell infiltrate								
very slight	0	0	0	1	0	0	0	0
slight	0	0	0	7 *	0	0	0	5*
moderate	0	0	0	1	0	0	0	1
Epithelial nest-like infolds	0	0	0	0	0	0	1	0
very slight	0	0	1	0	0	0	0	0
slight	0	0	15***	5	0	0	5	5*
moderate	0	0	1	5	0	0	0	2
Olfactory epithelial leukocytic exudate								
very slight	0	0	0	0	0	0	1	0
slight	0	0	0	11***	0	0	0	5 *
moderate	0	0	0	2	0	0	1	3
severe	0	0	0	1	0	0	0	0
Basal cell hyperplasia								
very slight	2	5	3	1	0	0	7*	0
slight	0	0	40***	21***	0	0	24***	35***
moderate	0	0	11***	22***	0	0	3	16***
severe	0	0	0	2	0	0	0	0
Turbinate leukocytic exudate								
very slight	0	2	0	0	1	1	3	1
slight	4	8	5	5	4	3	3	7
moderate	3	6	3	8	0	1	1	7 **
severe	0	0	0	1	0	0	0	0
Submucosal inflammatory cell infiltrate								
slight	2	0	1	2	0	0	0	0
moderate	1	3	1	6	0	0	0	5 *
severe	0	0	0	1	0	0	0	0
very severe	0	0	1	0	0	0	0	0

[a] Figures in parenthesis present the number of animals from which this tissue was examined microscopically. Significance of differences in a pairwise (Fisher´s) test between each treatment and control incidence is indicated by * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Cited from Bogdanffy et al. (1994b)

Table 2 : Summary of statistically significant non-neoplastic changes in lungs and nose of mice: main study
(EU Draft Risk Assessment Report, 2003)

	Incidence of Lesions Other than Tumors [a]							
	Males				Females			
Concentration (ppm):	Control	50	200	600	Control	50	200	600
Lungs:	(51)	(51)	(56)	(53)	(56)	(55)	(55)	(51)
Accumulation of alveolar macrophages								
very slight	5	1	4	3	5	2	6	1
slight	10	2 *	4	7	3	8	4	10
moderate	0	4	8 **	4	2	1	1	12 **
severe	1	1	4	0	1	3	1	1
Intra-alveolar eosinophilic material								
very slight	0	0	3	1	0	0	2	1
slight	3	1	1	19 ***	0	0	0	7 **
moderate	0	0	0	10 **	0	0	1	15 ***
severe	0	0	0	2	0	0	0	1
Accumulation of brown pigmented macrophages								
very slight	2	2	1	11 *	3	5	1	2
slight	0	0	5	12 ***	1	1	4	21 ***
moderate	0	0	1	1	0	0	0	2
Intraluminal fibroepithelial projections								
very slight	0	1	2	3	1	0	0	6
slight	0	0	0	17 ***	0	2	1	19 ***
moderate	0	0	0	3	0	0	0	7 **
Bronchial gland dilatation	14	16	26	17	8	17	20 *	15
Bronchial/bronchiolar epithelial flattening and/or exfoliation								
very slight	0	0	0	4	0	0	0	4 *
slight	1	0	0	25 ***	0	0	0	28 ***
moderate	0	0	0	7 *	0	0	0	4 *
severe	0	0	0	0	0	0	0	1
Bronchial/bronchiolar epithelial disorganization								
very slight	0	0	0	0	0	0	0	5 *
slight	0	0	0	11 **	0	1	0	18 ***
moderate	0	0	0	4	0	0	0	0

[a] Figures in parenthesis present the number of animals from which this tissue was examined microscopically. Significance of differences in a pairwise (Fisher´s) test between each treatment and control incidence is indicated by * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.
Cited from Bogdanffy et al. (1994b)

Table 2 (continued): Summary of statistically significant non-neoplastic changes in lungs and nose of mice: main study (EU Draft Risk Assessment Report, 2003)

	Incidence of Lesions Other than Tumors [a]							
	Males				Females			
Concentration (ppm):	Control	50	200	600	Control	50	200	600
Nose:	(52)	(48)	(53)	(50)	(56)	(57)	(55)	(51)
Inflammatory exudate	0	0	2	15***	0	0	1	5**
Mucosal inflammatory infiltrate	1	0	0	12**	1	2	0	5
Submucosal gland hyperplasia								
slight	3	3	28***	25***	2	5	42***	35***
moderate	0	0	8**	15***	0	0	7**	13***
Olfactory epithelial atrophy (mainly dorsal meatus)								
very slight	0	0	2	0	0	0	0	0
slight	0	0	5	0	2	4	8	0
moderate	0	0	28***	2	0	0	26***	0
severe	0	0	4	3	0	0	4	1
Olfactory epithelial atrophy (widespread)								
slight	0	0	1	0	0	0	0	0
moderate	1	0	8*	5	0	0	12***	5*
severe	0	0	4	39***	0	0	2	45***
Squamous metaplasia at the naso/maxilloturbinate region								
very slight	0	0	0	0	0	0	0	1
slight	1	1	2	13**	4	2	0	13*
moderate	0	1	0	11***	0	0	0	6**
severe	0	0	0	0	0	0	0	1
Replacement olfactory by respiratory epithelium								
slight	0	0	5	11***	0	0	15***	10***
moderate	0	0	1	0	0	1	5*	10***
severe	0	0	0	0	1	0	0	0
Trachea/bronchi:	(49)	(46)	(51)	(48)	(55)	(56)	(52)	(48)
Epithelial hyperplasia	0	0	2	19***	1	1	0	11***

[a] Figures in parenthesis present the number of animals from which this tissue was examined microscopically. Significance of differences in a pairwise (Fisher´s) test between each treatment and control incidence is indicated by * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Cited from Bogdanffy et al. (1994b)

Table 3: Incidence of tumours of the respiratory tract in Crl:CD(SR)BR rats after exposure to vinyl acetate (Bogdanffy *et al*. 1994b, as compiled by DFG 2002)

		0	50 ppm	200 ppm	600 ppm
Nasal cavity	♂	(59)	(60)	(59)	(59)
	♀	(60)	(60)	(60)	(59)
inverted papilloma	♂	0	0	0	4
	♀	0	0	0	0
papilloma	♂	0	0	1	0
	♀	0	0	0	0
squamous cell carcinoma	♂	0	0	0	2
	♀	0	0	0	4
carcinoma *in situ*	♂	0	0	0	1
	♀	0	0	0	0
sum of all tumours	♂	0	0	1	7[a]
	♀	0	0	0	4
Larynx	♂	(59)	(60)	(60)	(60)
	♀	(60)	(60)	(60)	(59)
squamous cell carcinoma	♂	0	0	0	0
	♀	0	0	0	1

[a] $p < 0.01$, Fisher's exact test
number of animals investigated in brackets