The MAK-Collection for Occupational Health and Safety

GMS PUBLISSO ZB MED-Publikationsportal Lebenswissenschaften

# Vinyl acetate

## MAK Value Documentation, supplement – Translation of the German version from 2020

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**Keywords**

vinyl acetate; nose; irritation; carcinogenicity; reproductive toxicity; genotoxicity; metabolism; maximum workplace concentration; MAK value; ceiling limit value

## Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated vinyl acetate [108-05-4]. The critical effects are nasal irritation and the induction of nasal tumours observed in a 2-year study in rats. From mechanistic studies it was concluded that acidification by acetic acid formed metabolically from vinyl acetate is responsible for the cell proliferation in the nasal epithelia and probably also for clastogenicity and DNA strand breaks. Acetaldehyde formed from vinyl acetate induces DNA-protein cross-links and clastogenicity. The DNA damage can lead to tumours after cell proliferation which is induced at cytotoxic concentrations of vinyl acetate. Non-linear dose-response curves were obtained in several carcinogenicity studies as well as in genotoxicity studies in vitro. This implies that the genotoxicity of vinyl acetate is not primarily responsible for the induction of nasal tumours. As they occurred only at concentrations that damaged the nasal epithelia of rats and NOAECs for this effect as well as for acidification in the nasal epithelia and for sensory irritation in humans could be derived, vinyl acetate has been classified in Carcinogen Category 4. According to a PBPK model, the NOAEC for acidification in the nasal epithelia of humans at the workplace is 19 ml/m$^3$. In volunteer studies with limited validity, slight sensory irritation was observed at 20 ml/m$^3$. Therefore, a maximum concentration at the workplace (MAK value) of 10 ml/m$^3$ has been derived for vinyl acetate. As the critical effect is local irritation, the substance has been assigned to Peak Limitation Category I. To avoid local irritation by short-term peaks, an excursion factor of 2 and a momentary value of 20 ml/m$^3$ have been set. The NOAEC for developmental toxicity in rats of 200 ml/m$^3$ and the NOAEL of 477 mg/kg body weight obtained from a 2-generation study are sufficiently high. Therefore, damage to the embryo or foetus is unlikely when the MAK value is not exceeded and vinyl acetate is classified in Pregnancy Risk Group C. Vinyl acetate is clastogenic in vitro. It is a clastogen in vivo when given intraperitoneally at high doses but not after inhalation or when administered with the drinking water. It did not induce micronuclei in spermatids of rats. According to the results of an in vitro study, vinyl acetate is labelled with "H" for substances which can be taken up via the skin in toxicologically relevant amounts. There are no data that show that vinyl acetate is a skin or airway sensitizer.

Citation Note:
Hartwig A, MAK Commission. Vinyl acetate. MAK Value Documentation, supplement – Translation of the German version from 2020. MAK Collect Occup Health Saf. 2022 Dec;7(4):Doc077. https://doi.org/10.34865/mb10805e7_4ad

Manuscript completed:
26 Mar 2019

Publication date:
19 Dec 2022

| | |
|---|---|
| **MAK value (2019)** | **10 ml/m³ (ppm) ≙ 36 mg/m³** |
| **Peak limitation (2019)** | **Category I, excursion factor 1** |
| **Momentary value (2019)** | **20 ml/m³ (ppm) ≙ 71 mg/m³** |
| **Absorption through the skin (2019)** | **H** |
| **Sensitization** | **–** |
| **Carcinogenicity (2019)** | **Category 4** |
| **Prenatal toxicity (2019)** | **Pregnancy Risk Group C** |
| **Germ cell mutagenicity** | **–** |
| **BAT value** | **–** |
| CAS number | 108-05-4 |
| Molar mass | 86.09 g/mol |
| Solubility at 20 °C | 20 g/l water (ECHA 2019) |
| log $K_{OW}$ at 25 °C | 0.73 (ECHA 2019) |
| Vapour pressure at 20 °C | 113 hPa (ECHA 2019) |
| **1 ml/m³ (ppm) ≙ 3.572 mg/m³** | **1 mg/m³ ≙ 0.280 ml/m³ (ppm)** |

There is documentation from 1983 and supplements from 1991, 2000 and 2002 (published in two combined translations: Greim 2005; Henschler 1993). The reason for this supplement is the re-evaluation of the carcinogenicity of vinyl acetate with the derivation of a MAK value.

# 1 Toxic Effects and Mode of Action

Vinyl acetate is very readily absorbed and metabolized by the epithelia of the nasal cavity. In the organism, vinyl acetate is enzymatically hydrolysed to acetaldehyde and acetic acid. Acetaldehyde is oxidized to acetic acid, which ultimately enters the C2 intermediary metabolism.

Vinyl acetate is of low acute toxicity after oral and dermal exposure, whereas higher inhaled concentrations are acutely toxic. After single exposures, vinyl acetate as a liquid is not irritating to the skin or eyes of rabbits. However, the substance may be irritating to corrosive to the skin and irritating to the eyes after prolonged exposure. Slight irritation in the throat was reported by 1 of 4 volunteers after exposure to a concentration of about 20 ml/m³ for 4 hours.

Cell proliferation of the oral mucosa and the respiratory and olfactory epithelium occurred after repeated oral or inhalation exposure. Vinyl acetate leads to DNA–protein cross-linking in vitro. This effect is attributed to the metabolite acetaldehyde. In the Salmonella mutagenicity test the substance was not mutagenic. The results for vinyl acetate were positive in the micronucleus test, the chromosomal aberration test and the sister chromatid exchange (SCE) test in vitro. After administration in drinking water, vinyl acetate led to local tumours on the tongue and in the mouth, oesophagus and stomach of rats and mice. In rats, after inhalation exposure to a vinyl acetate concentration of 600 ml/m³ for 2 years, there was an increased incidence of nasal tumours and, at 200 ml/m³ and above, non-neoplastic nasal damage.

In a developmental toxicity study in rats, the maternally toxic concentration of 1000 ml/m$^3$ resulted in decreased body weights in the foetuses, a shortened mean crown-rump length and an increased frequency of skeletal variations, mostly ossification delays.

The few indications of a sensitizing effect of vinyl acetate (Greim 2005) are not reliable.

## 2 Mechanism of Action

The critical effect is the local carcinogenic effect and irritation of the nasal epithelia. Vinyl acetate is clastogenic.

Vinyl acetate is metabolized in the nasal tissue by carboxylesterases to acetaldehyde and acetic acid. Acetaldehyde is also further oxidized to acetic acid. This produces a total of 3 protons per molecule of vinyl acetate. If the vinyl acetate concentration is high enough, the intracellular buffer capacity is exceeded and the intracellular pH decreases. This leads to mitogenic cell proliferation in the respiratory epithelium, which is relatively insensitive to cytotoxicity, and cytotoxic cell proliferation in the olfactory epithelium. Organic acids can be clastogenic and lead to topoisomerase II-induced DNA strand breaks. In addition, the resulting acetaldehyde can cause DNA–protein crosslinks and clastogenic effects. This damage manifests itself with increased cell proliferation as tumours (Bogdanffy and Valentine 2003; Hinderliter et al. 2005).

After the exposure of respiratory and olfactory nasal epithelial cells of rats to vinyl acetate, intracellular acidification was demonstrated. The concentrations used were 100 to 1000 µM vinyl acetate for up to 4 minutes. In the respiratory epithelial cells, the maximum drop in pH was 0.3 units at 250 µM, where it reached a plateau. In olfactory epithelial cells, two populations were distinguished, only one of which reacted to vinyl acetate. Here, the drop in pH did not reach a plateau. The carboxylesterase inhibitor bis(*p*-nitrophenyl)phosphate reduced the drop in pH. Tests with nasal tissue samples from rats confirmed the results (Lantz et al. 2003).

Intracellular acidification was demonstrated also in vitro with oral mucosal cells of the mouse. The concentrations used were 10 to 1000 µM vinyl acetate for up to 4 minutes. The acidification increased exponentially with the increasing concentration and could be inhibited by a carboxylesterase inhibitor (Nakamoto et al. 2005).

The concentration–response relationship in rats in the carcinogenicity study by Bogdanffy et al. (1994) suggests a non-linear dependence of nasal carcinomas on the vinyl acetate concentration, although the small number of animals does not allow a reliable conclusion (Figure 1).

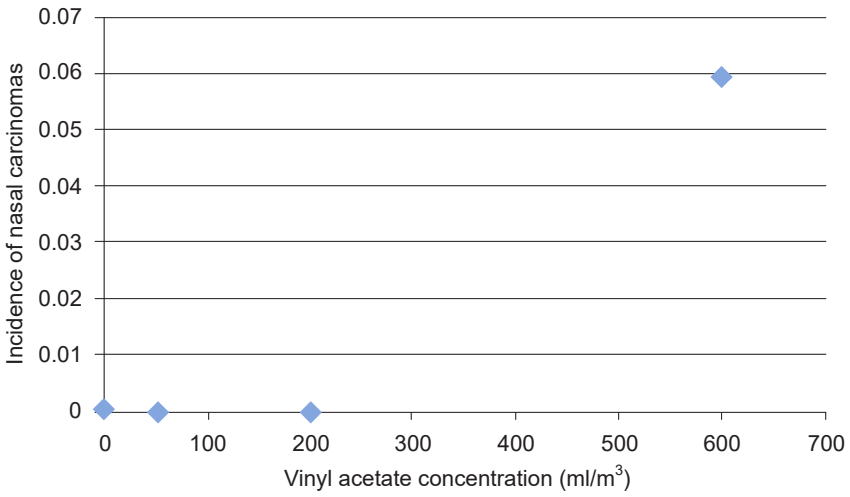


**Fig. 1** Concentration–response relationship for nasal epithelial carcinomas in rats in the inhalation carcinogenicity study with vinyl acetate (Bogdanffy et al. 1994; Greim 2005), male and female rats evaluated together

However, non-linear concentration–response relationships were observed also for tumours in the oral cavity, oesophagus and forestomach after administration with the drinking water, especially in mice. However, it was unclear whether the non-linear concentration–response relationship for tumours can be attributed solely to the enhancing effect of the cytotoxicity and mitogenicity of acetic acid and whether these mechanisms are decisive compared with the genotoxic effect (Greim 2005).

A non-linear concentration–response relationship was found also for mutations and micronuclei in human TK6 cells in vitro (Section 5.6.1). It can therefore be assumed that genotoxicity occurs only at concentrations that overwhelm the cellular detoxification mechanisms (above all aldehyde dehydrogenase 2) and that the cytotoxic and mitogenic effect of acidification by the resulting acetic acid has an amplifying effect that leads to tumours through increased cell proliferation.

Based on the data for metabolism, toxicokinetics, genotoxicity and carcinogenicity, vinyl acetate was evaluated as a genotoxic substance with a "practical threshold" (Bogdanffy and Valentine 2003; Hengstler et al. 2003; Slikker et al. 2004).

# 3 Toxicokinetics and Metabolism

## 3.1 Absorption, distribution, elimination

The blood:air partition coefficient for rats is 29 (Plowchalk et al. 1997). Therefore, for systemic effects in animal experiments, the increased respiratory volume at the workplace compared with that of laboratory animals at rest has to be taken into account (DFG 2019, Section I b and I c).

A physiologically based pharmacokinetic (PBPK) model has been developed for vinyl acetate (Andersen et al. 2002; Bogdanffy et al. 1999). In the 2002 supplement it was shown that, according to the model, a significant drop in pH (0.07 units) in the olfactory epithelium of the rat which leads to damage in the nasal epithelium is only to be expected at vinyl acetate concentrations of more than 50 ml/m$^3$. The data were extrapolated to humans using a PBPK model. However, the validity of various assumptions of this model was criticized (Greim 2005). A concentration of 19 ml/m$^3$ was calculated for humans under workplace exposure conditions (respiratory volume 20 l/min) which leads to a drop in pH by 0.07 units. The authors concluded from this that a limit value of 10 ml/m$^3$ at the workplace provides sufficient protection against acidification and thus against mitogenic effects and damage to the nasal epithelia caused by the acetic acid formed (Bogdanffy et al. 1999).

In the meantime, the PBPK model has been validated. For this purpose, 5 volunteers were exposed to radioactively labelled vinyl acetate concentrations of 1, 5 or 10 ml/m$^3$ via the nose for 2 to 5 minutes at rest or during light exercise (50 watts on a bicycle ergometer). A catheter connected to a mass spectrometer was located in the nasopharyngeal region of the test persons. This allowed the nasopharyngeal concentrations of vinyl acetate and the metabolically formed acetaldehyde to be determined and compared with the predictions of the model by Bogdanffy et al. (1999). The concentration of vinyl acetate in the nasopharyngeal space was about 40% of the external concentration and that of acetaldehyde was on average about 20% of the external concentration of vinyl acetate. The difference between the respective concentrations at rest and during light exercise was small. The measured concentrations were in good agreement with the concentrations predicted by the model, thus reflecting well the deposition of vinyl acetate and the metabolism to acetaldehyde. Thus, the model is valid. According to the authors, this confirms the assumption of an acceptable workplace concentration of 10 ml/m$^3$ in the publication by Bogdanffy et al. (1999) (Hinderliter et al. 2005).

Using the PBPK model, it was calculated that a vinyl acetate concentration of 50 ml/m$^3$ results in an acetaldehyde concentration of 1.7 µg/ml (39 µM) in the basal cells of the olfactory epithelium of rats. Nasal tumours originate from these basal cells (Bogdanffy and Valentine 2003; Slikker et al. 2004). This concentration is below the NOAEC (no observed adverse effect concentration) for mutagenic effects caused by acetaldehyde (2.2 µg/ml; 50 µM) in human TK6 cells (Section 5.6.1). Using the PBPK model, it was calculated that continuous exposure to a vinyl acetate concentration of

1 ml/m$^3$ leads to an acetaldehyde concentration of 0.1 µg/ml in human olfactory basal cells (Bogdanffy and Valentine 2003; Slikker et al. 2004). After linear extrapolation, the NOAEC for the genotoxicity of acetaldehyde in TK6 cells would not be exceeded at 10 ml/m$^3$ in humans (1 µg/ml; 23 µM). The background concentration of acetaldehyde in the olfactory basal cells of rats and humans is not known. The background concentration of acetaldehyde in human blood is 2.2 µM (0.1 µg/ml) (Hartwig 2013). The endogenous concentration of acetaldehyde in rat blood is about 1 µM (0.044 µg/ml), although its determination, like in human blood, is difficult (Eriksson 1985).

Assuming that the water-miscible acetaldehyde has the same concentration in all body cells as in the blood, the background concentration in the olfactory basal cells in rats is about 1 µM (0.044 µg/ml). The PBPK model predicts that a vinyl acetate concentration of 50 ml/m$^3$ leads to an acetaldehyde concentration of 1.7 µg/ml (39 µM) in the olfactory basal cells of rats, about 39 times the background concentration. However, this external concentration of 50 ml/m$^3$ did not lead to damage of the olfactory epithelium in the long-term study with rats, and nasal carcinomas did not occur even at 200 ml/m$^3$. This means that even 39 times the background concentration of acetaldehyde can still be compensated for, or if acetaldehyde is continuously formed from vinyl acetate in vivo, it is directly metabolized further and thus a critical concentration of acetaldehyde is not formed in the cell at 50 ml vinyl acetate/m$^3$. Under the experimental conditions of animal studies, the AUC (area under the curve) of acetaldehyde after 6 hours exposure to 50 ml vinyl acetate/m$^3$ for 5 days per week is 7 times (39 × (6 hours/24 hours) × (5 days/7 days)) the endogenous continuous exposure to acetaldehyde. It can therefore be assumed that neither the formation of acetaldehyde nor that of acetic acid is sufficient to cause damage to the olfactory epithelium following exposure to 50 ml vinyl acetate/m$^3$. Since tumours caused by vinyl acetate occur only at concentrations that lead also to toxicity, protection against the cytotoxic effect is also protection against nasal tumours.

For a saturated aqueous solution, the model of Fiserova-Bergerova et al. (1990) and the algorithm of the IH SkinPerm model (Tibaldi et al. 2014) calculate fluxes of 289 and 47.4 µg/cm$^2$ and hour, respectively. Assuming the exposure of 2000 cm$^2$ of skin (area of hands and forearms) for 1 hour, this would correspond to absorbed amounts of 578 and 94.8 mg, respectively.

With exposure to gaseous vinyl acetate at the level of the MAK value of 10 ml/m$^3$, taking into account Henry's constant ($H_{pc}$) of approximately $1.7 \times 10^{-2}$ mol/m$^3$/Pa (Sander 2015) the concentration in an aqueous film on the skin surface is 0.00146 g/l. According to the above models, at this concentration, exposure of the whole body (18 000 cm$^2$) for 8 hours would result in a maximum amount of 3 mg vinyl acetate absorbed through the skin.

### 3.2 Metabolism

Vinyl acetate is metabolized in the nasal tissue by carboxylesterases to acetic acid and vinyl alcohol, which rearranges to acetaldehyde. Acetaldehyde is also further oxidized to acetic acid. This produces a total of three protons per molecule of vinyl acetate (Bogdanffy and Valentine 2003; Hinderliter et al. 2005).

The cleavage of vinyl acetate is carried out by carboxylesterases, the detoxification of acetaldehyde by aldehyde dehydrogenase 2. Metabolism to the epoxide takes place only in very small quantities and is therefore of no importance for the carcinogenic and mutagenic effects (Albertini 2013).

## 4 Effects in Humans

The studies listed below and in Table 1 were described in summary form in the previous documentation and supplements and are now presented in detail. There are no new findings in humans or for other end points.

During the sampling for the workplace study described below, 5 persons (1 of the authors, 1 technician and 1 employee from each of the 3 production units investigated) reported on their subjective perception of irritation. A total of thirteen 10-minute samples were taken in the 3 production units. At the highest determined 10-minute concentration of 21.6 ml/m$^3$ in 1 of the 3 production units, all 3 exposed persons experienced irritation of the eyes and coughing.

This concentration was assessed as not tolerable for an 8-hour exposure period. In 12 further samples with 10-minute mean values of 0.4 to 10 ml/m³, eye irritation was reported in only 1 person in 2 samplings at about 6 ml/m³, but not at lower and higher concentrations. Thus, no concentration-dependent symptoms occurred up to 10 ml/m³ in a total of 5 persons. At about 2 ml/m³ and above, the odour of vinyl acetate was perceptible. The authors concluded that 10 ml/m³ did not cause irritation in most people (Deese and Joyner 1969; Henschler 1993). The occurrence of exposure peaks during the 10-minute sampling period at about 6 ml/m³ could have caused the irritant effect in 1 person. This is supported by the fact that this person reported no irritant effects at higher concentrations of up to 10 ml/m³.

In a study, slight persistent irritation in the throat was reported by 1 of 3 subjects after controlled exposure to 19.5 ml/m³ for 4 hours. The concentration of 22.9 ml/m³ remained without irritant effects in 1 exposed person. At 34.2 ml/m³, in 2 of 3 exposed persons, transient or persistent irritation in the throat was found. No eye irritation occurred up to this concentration. After exposure to 71.5 ml/m³ for 30 minutes, all 4 exposed persons experienced irritation of the throat and eyes. This concentration was not considered tolerable for an 8-hour exposure period (NIOSH 1978; Union Carbide 1973). After a 2-minute exposure, 1 of 9 persons reported minimal eye, nose and throat irritation at 4, 8 and 20 ml/m³, respectively. At 1.3 ml/m³ no irritation was observed. A control exposure was not performed (Union Carbide 1973). The data show that there may be minor effects at around 20 ml/m³, as only 1 of 4 persons reported slight throat irritation. When the data for the 2-minute exposure are compared with those for the 4-hour exposure it is apparent that there was only a slight increase in symptoms.

The results of the two studies are contradictory as regards eye irritation, as the NOAEC was 10 ml/m³ in one study and 34 ml/m³ in the second. The exposed persons in the first study reported that exposure to 20 ml/m³ for 10 minutes caused intolerable eye irritation in all of them, whereas in the controlled study, exposure to similar concentrations for 4 hours did not cause eye irritation but slight throat irritation in 1 of 4 subjects. The reason for this discrepancy is thought to be the occurrence of exposure peaks during determinations at the workplace in the study by Deese and Joyner (1969). This study is therefore not included in the assessment of the irritant effects of vinyl acetate.

No irritation was observed at workplace concentrations of 0.4 to 4.9 ml vinyl acetate/m³ (NIOSH 1978).

**Tab. 1** Human findings regarding the irritant effects of vinyl acetate

| Concentration (ml/m³) | Time | Number of persons | Findings | References |
|---|---|---|---|---|
| 0.4–10 | 10 minutes | 5 | 5/5: NOAEC | Deese and Joyner 1969 |
| 6<br>additional exposure peaks? | 10 minutes | 5 | 1/5: eye irritation | |
| 4–20 | 2 minutes | 9 | 1–2/9: minimal irritation of eyes, nose and throat | Union Carbide 1973 |
| 19.5 | 4 hours | 3 | 1/3: slight irritation of throat | NIOSH 1978; Union Carbide 1973 |
| 21.6<br>additional exposure peaks? | 10 minutes | 3 | 3/3: irritation of eyes and throat, intolerable for 8-hour exposure period | Deese and Joyner 1969 |
| 22.9 | 4 hours | 1 | 1/1: NOAEC | NIOSH 1978; Union Carbide 1973 |
| 34.2 | 2 hours | 3 | 2/3: irritation of throat | |
| 71.5 | 30 minutes | 4 | 4/4: irritation of eyes and throat, intolerable for 8-hour exposure period | |
| 0.4–4-9 | "at the workplace"; no other details | | no irritation, irritation occurred after spills | NIOSH 1978 |
| 5.2–8.2<br>exposure peaks up to 49.3 | 8-hour mean values | | no systemic findings, some reported eye irritation (not possible to assign effects to exposure) | Deese and Joyner 1969 |

No substance-related systemic complaints and findings were recorded in 21 workers occupationally exposed to vinyl acetate, compared with in age-matched workers of the same company who were not exposed to vinyl acetate. Some

exposed workers reported eye irritation. The concentrations (8-hour averages) were in the range between 5.2 and 8.2 ml/m$^3$. The 10-minute short-term values were 0 to 49.3 ml/m$^3$ and during maintenance work up to 326.5 ml/m$^3$ (Deese and Joyner 1969; Henschler 1993) The irritant effects were not attributable to any concentration, so that a NOAEC could not be derived.

# 5 Animal Experiments and in vitro Studies

## 5.1 Acute toxicity

One beagle dog per concentration was exposed to 62.5, 125, 250, 1000, 2000 or 4000 ml vinyl acetate/m$^3$ for 4 hours. At concentrations of 250 ml/m$^3$ and above, eye irritation (blinking, reddening of the sclera) occurred. At higher concentrations, the irritant effects were severe (lacrimation, inflamed eyelids, nasal discharge). Exposure to concentrations of 62.5 and 125 ml/m$^3$ did not have any visible irritant effects (Union Carbide 1973).

An $RD_{50}$ in mice of 380 ml vinyl acetate/m$^3$ was reported in an abstract (Dudek et al. 1996). A detailed publication is not available.

## 5.2 Subacute, subchronic and chronic toxicity

In 2-year studies with inhalation exposure of rats and mice, the NOAEC for local and systemic effects was 50 ml/m$^3$ for both species. At the concentration of 200 ml/m$^3$, delayed body weight gains were observed in mice and histological changes in the olfactory epithelium (atrophy, regeneration, nest-like infolds) based on irritant effects were found in rats and mice. At 600 ml/m$^3$, irritation of the trachea and lungs and, in rats, reduced body weights and increased incidences of nasal tumours were observed (Greim 2005).

## 5.3 Local effects on skin and mucous membranes

### 5.3.1 Skin

In an unpublished test carried out according to OECD Test Guideline 404, the skin irritation caused by vinyl acetate was investigated in rabbits. There were transient signs of irritation. The readings after 24, 48 and 72 hours yielded average irritation scores of 0.33 for erythema and 0 for oedema, which did not lead to classification as a skin irritant (ECHA 2019).

### 5.3.2 Eyes

In an unpublished test carried out according to OECD Test Guideline 405, eye irritation was evaluated in rabbits 1, 24, 48 and 72 hours after the instillation of vinyl acetate. One hour after exposure there were transient signs of irritation such as moderate redness of the conjunctiva and sclera, slight discharge and mild to moderate chemosis. The readings after 24, 48 and 72 hours yielded average irritation scores of 0.33, which did not lead to classification as an eye irritant (ECHA 2019).

## 5.4 Allergenic effects

### 5.4.1 Sensitizing effects on the skin

The clearly negative result of a local lymph node assay in female CBA/Ca mice confirms that vinyl acetate does not have skin sensitizing potential. The vinyl acetate concentrations used in acetone/olive oil (4:1) were 5%, 10%, 25% and 50%. Undiluted vinyl acetate was also tested. The stimulation indices obtained with these preparations were 2.0, 2.4, 1.9, 1.7 and 1.3, respectively, so that none of the test preparations led to a tripling of lymphocyte proliferation (ECHA 2019).

### 5.4.2 Sensitizing effects on the airways

There are no data available.

## 5.5 Reproductive and developmental toxicity

### 5.5.1 Fertility

In a 2-generation study, groups of 18 male and 36 female Crl:CD(SD)BR rats received vinyl acetate in concentrations of 0, 200, 1000 or 5000 mg/l drinking water (for male animals, for the entire treatment period, equivalent to doses of: 0, 20, 100, 450 mg/kg body weight and day; for female animals before mating: 0, 30, 135, 550 mg/kg body weight and day; during gestation: 0, 38, 170, 671 mg/kg body weight and day in the F0 generation and 0, 38, 166, 648 mg/kg body weight and day in the F1 generation; during lactation: 0, 56, 271, 1158 mg/kg body weight and day in the F0 generation and 0, 55, 262, 1231 mg/kg body weight and day in the F1 generation). At 1000 mg/l and above, the water consumption of the female F1 animals and their body weight gains during lactation were reduced. In the 5000 mg/l group, the water consumption of males and females was reduced in both generations before mating. The body weights of the male F0 and F1 animals and the female F1 rats and the body weight gains during lactation were decreased in the F0 animals. In the high-dose group, the number of litters was slightly reduced. The weights of the F1 but not the F2 pups were reduced on lactation day 21. Cross-mating of the males in the high dose group with untreated animals resulted in fewer litters, which was not due to reduced fertility but to poor mating performance. The authors considered 1000 mg/l as the NOAEL (no observed adverse effect level) for all effects (Mebus et al. 1995). The study was already described in the 1991 supplement (Henschler 1993) as an unpublished study.

### 5.5.2 Developmental toxicity

Groups of 23 or 24 Crl:CD(SD)BR rats were exposed to vinyl acetate concentrations of 0, 200, 1000 or 5000 mg/l in the drinking water (0, 28, 124, 477 mg/kg body weight and day) or by inhalation to 0, 50, 200 or 1000 ml/m$^3$ for 6 hours daily from days 6 to 15 of gestation. The administration of vinyl acetate with the drinking water did not cause developmental or maternal toxicity up to the highest dose tested. In the dams of the 477 mg/kg group water consumption was reduced, reflecting the unpalatability of the vinyl acetate solution in this dose group. The inhalation study revealed a statistically significant decrease in the mean body weight and mean crown-rump length in the foetuses at 1000 ml/m$^3$, as well as a statistically significant increase in the frequency of skeletal variations, mostly ossification delays. At the same time, maternal toxicity occurred in the form of reduced body weight gains. The NOAEC for developmental toxicity in the inhalation study was 200 ml/m$^3$, the NOAEL in the drinking water study 477 mg/kg body weight and day (Hurtt et al. 1995). The study was already described as an unpublished study in the 1991 supplement (Henschler 1993).

In a 2-generation study (see Section 5.5.1), Crl:CD(SD)BR rats received vinyl acetate in concentrations of 0, 200, 1000 or 5000 mg/l drinking water (for females, before mating, equivalent to doses of: 0, 30, 135, 550 mg/kg body weight and day; during gestation: 0, 38, 170, 671 mg/kg body weight and day in the F0 generation and 0, 38, 166, 648 mg/kg body weight and day in the F1 generation; during lactation: 0, 56, 271, 1158 mg/kg body weight and day in the F0 generation and 0, 55, 262, 1231 mg/kg body weight and day in the F1 generation). Up to the highest dose tested during gestation of 671 and 648 mg/kg body weight and day for the F0 and F1 dams, respectively, no perinatal toxicity was observed in

the offspring until postnatal day 7. The body weights and drinking water consumption of the dams were reduced at the middle dose (170 mg/kg body weight and day for the F0 generation and 166 mg/kg body weight and day for the F1 generation during gestation) and above. The NOAELs for perinatal toxicity are thus 671 and 648 mg/kg body weight and day for the F0 and F1 generations, respectively (Mebus et al. 1995).

## 5.6 Genotoxicity

The data available for the genotoxicity of the substance have already been summarized in the 2002 supplement (Greim 2005) and in the review of Albertini (2013). In the following, relevant studies published after 2003 are described.

### 5.6.1 In vitro

In a Salmonella mutagenicity test using the metabolically competent strain YG7108pin3Erb$_5$, which expresses cytochrome P450 2E1, vinyl acetate was not found to be mutagenic up to the highest concentration tested of 2000 µg/plate. The investigated substances were tested up to the solubility or toxicity limit or up to 5000 µg/plate (Emmert et al. 2006). It was pointed out that vinyl acetate must be cleaved by carboxylesterases in order to produce mutagenic effects via acetaldehyde, although it is questionable whether carboxylesterases were present in the system used. However, acetaldehyde itself is not mutagenic in the Salmonella mutagenicity test, which is due to cytotoxicity, as the crosslinks that occur are not mutagenic but toxic for the bacteria (Norppa 2007).

In the in vitro test systems used in the TOXCAST project, there was no evidence of a p53-mediated transcriptional response that could be interpreted as a response to DNA damage. A reduced adenosine triphosphate content in a human cell line was found, however, indicating cytotoxicity. Test results for other end points were negative (US EPA 2020).

Using human TK6 lymphoblastoid cells, vinyl acetate was investigated for the formation of micronuclei and thymidine kinase (TK) mutants. Only when using serum, which metabolizes vinyl acetate to acetaldehyde, was an increase in the micronucleus frequency observed. Mutations at the TK locus occurred when hydrolysis was sufficiently rapid. These genotoxic effects were observed only at concentrations of 250 µM vinyl acetate and above. Also for acetaldehyde the concentration of 250 µM was the LOAEC (lowest observed adverse effect concentration) for micronucleus formation and about 50 to 100 µM was the LOAEC for TK mutations. Neither vinyl acetate nor acetaldehyde induced mutations at the HPRT locus. The NOAEC for micronucleus formation was 50 µM for both vinyl acetate and acetaldehyde. At this concentration the micronucleus frequency was in the range of the historical controls. The authors concluded there to be a non-linear concentration–response curve for the mutagenicity and clastogenicity of both substances. Acetic acid at a concentration of 10 mM caused a decrease in the pH in the medium, but did not lead to the formation of micronuclei (Budinsky et al. 2013).

The concentration–response curves suggest that at 50 µM vinyl acetate or acetaldehyde these genotoxic effects are not increased above background levels.

**Summary:** At higher concentrations vinyl acetate leads to DNA–protein cross-linking in vitro. This effect is attributed to the metabolite acetaldehyde. In the Salmonella mutagenicity test the substance was not mutagenic. Positive test results with vinyl acetate were obtained in the micronucleus test, chromosomal aberration test and SCE test in vitro (Greim 2005). New studies revealed a non-linear concentration–response curve for mutagenicity and clastogenicity with a NOAEC for micronucleus formation of 50 µM for both vinyl acetate and acetaldehyde.

### 5.6.2 In vivo

In vivo, micronuclei and SCE were observed at very high single intraperitoneal doses in bone marrow cells of mice, but not after inhalation exposure or after the administration of vinyl acetate in drinking water. An in vivo micronucleus test in germ cells (spermatids) yielded negative results (Greim 2005).

There are no new data available.

### 5.6.3 Assessment of genotoxicity

The genotoxicity assessment from Greim (2005) is given below.

Comparative in vitro studies with acetaldehyde indicate that the genotoxic effects of vinyl acetate are to be attributed to the metabolite acetaldehyde. The clastogenic effects resulting from a drop in pH seem to be less important. 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 saturation of inactivation mechanisms. At high doses, clastogenic effects of vinyl acetate (induced by the metabolite acetaldehyde or a drop in pH) on tissues directly exposed locally cannot be excluded. These clastogenic effects may be enhanced as a result of proliferative reactions caused by acetic acid-induced pH shifts. With regard to the metabolic formation of acetaldehyde, the detoxification capacity of the organism and the endogenous background presence of ethanol and acetaldehyde must be borne in mind. In this respect, reference is made to the documentation for ethanol (Greim 1999).

## 5.7 Carcinogenicity

There are no new studies available.

The decisive study by Bogdanffy et al. (1994) was already described in the 2002 supplement (Greim 2005). After 2 years of inhalation exposure, increased incidences of nasal tumours occurred in rats only in the high concentration group of 600 ml/m$^3$. In mice exposed under the same conditions to the same concentrations, tumour incidences were not increased.

**Tab. 2** Incidences of tumours of the respiratory tract in Crl: CD(SR)BR rats after inhalation exposure to vinyl acetate for 2 years (Bogdanffy et al. 1994)

| | | Concentration (ml/m$^3$) | | | |
|---|---|---|---|---|---|
| | | **0** | **50** | **200** | **600** |
| **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 tumours | ♂ | 0 | 0 | 1 | 7* |
| | ♀ | 0 | 0 | 0 | 4 |
| **Larynx** | ♂ | (59) | (60) | (60) | (60) |
| | ♀ | (60) | (60) | (60) | (59) |
| squamous cell carcinoma | ♂ | 0 | 0 | 0 | 0 |
| | ♀ | 0 | 0 | 0 | 1 |

*$p < 0.01$, Fisher's exact test, number of animals examined in brackets

The unpublished carcinogenicity study in rats and mice from Japan with administration of vinyl acetate in concentrations of 400, 2000 or 10 000 mg/l drinking water, which was already described in the last supplement, has now been published (Umeda et al. 2004).

There is a new study by the Ramazzini Institute in Sprague Dawley rats with vinyl acetate. Seventeen-week-old rats and 12-day-old embryos (presumably in utero exposure via the dams; no other details) were given drinking water containing vinyl acetate concentrations of 0, 1000 or 5000 mg/l. The animals were observed until their natural death.

The incidences of carcinomas of the oral cavity, lips, tongue, oesophagus and forestomach were increased. Another study was conducted with Wistar rats and announced for publication (Minardi et al. 2002). This study confirmed the local carcinogenic effects of vinyl acetate already known from other studies with oral administration.

# 6 Manifesto (MAK value/classification)

The critical effects are sensory irritation and local carcinogenicity in the nose.

**Carcinogenicity.** Until recently, it was not clear whether cytotoxicity or genotoxicity is the main factor for the carcinogenicity of the substance. Vinyl acetate is continuously metabolized in the nasal tissue by carboxylesterases to form acetaldehyde and acetic acid. Acetaldehyde is further oxidized to acetic acid, which ultimately enters the C2 intermediary metabolism. This produces a total of 3 protons per molecule of vinyl acetate. If the vinyl acetate concentration is high enough, the intracellular buffer capacity is exceeded and the intracellular pH decreases. This leads to mitogenic cell proliferation in the respiratory epithelium, which is relatively insensitive to cytotoxic effects, and cytotoxic cell proliferation in the olfactory epithelium. Organic acids can be clastogenic and cause topoisomerase II-induced DNA strand breaks. In addition, the resulting acetaldehyde can cause DNA–protein crosslinks and clastogenic effects. This damage manifests itself as increased cell proliferation associated with tumour formation (Bogdanffy and Valentine 2003; Hinderliter et al. 2005).

An in vitro study has now demonstrated a non-linear concentration–response relationship for the mutagenic and clastogenic effects, so that a NOAEC can be assumed also for genotoxicity. A non-linear concentration–response relationship of vinyl acetate has been shown in many carcinogenicity studies. As tumours in the nose occurred only at toxic concentrations, genotoxicity cannot be solely responsible for the tumours.

Since a MAK value can be derived which protects against sensory irritation and thus toxicity in the nasal epithelium and against genotoxic effects, vinyl acetate can be reclassified in Carcinogen Category 4.

**MAK value.** In a study conducted in volunteers after the publication of the last supplement, the concentration of acetaldehyde formed in the nasal cavity after exposure to vinyl acetate at concentrations of 1, 5 or 10 ml/m$^3$ was investigated (Hinderliter et al. 2005). It was found that the acetaldehyde concentration was in good agreement with the predictions of the PBPK model (Bogdanffy et al. 1999).

For long-term inhalation exposure, the NOAEC for local and systemic effects is 50 ml/m$^3$ in both rats and mice. The extrapolation of the NOAEC for the olfactory epithelium of rats to humans (1:2) according to Brüning et al. (2014) would suggest a MAK value of 20 ml/m$^3$ for vinyl acetate. With regard to acidification in the human nasal epithelium, PBPK modelling yields a threshold limit value for occupational exposure of 19 ml/m$^3$, as no significant drop in pH is yet to be expected at this concentration. At about 20 ml/m$^3$, however, slight sensory irritation was reported by 1 of 4 volunteers after exposure for 4 hours (NIOSH 1978; Union Carbide 1973). Therefore, a MAK value of 10 ml/m$^3$ has been set. The irritant effect after exposure for 4 hours is not significantly stronger compared with that after exposure for 2 minutes. It is therefore expected that after 8 hours of exposure the effects will not further increase. The $RD_{50}$ of 380 ml/m$^3$ in mice does not speak against the MAK value of 10 ml/m$^3$ according to the empirical relationship $RD_{50} \times 0.03 =$ limit value (Schaper 1993).

For the metabolites acetaldehyde (MAK value 50 ml/m$^3$) and acetic acid (MAK value 10 ml/m$^3$), valid volunteer studies of sensory irritation are available, which yielded a NOAEC of 50 ml/m$^3$ after exposure for 4 hours for acetaldehyde (Muttray et al. 2009) and 10 ml/m$^3$ for acetic acid (Hartwig 2010). For methyl acetate and ethyl acetate, which like vinyl acetate metabolically release acetic acid, the MAK values (methyl acetate: 100 ml/m$^3$, ethyl acetate: 200 ml/m$^3$) are higher than that for acetic acid itself. Ethanol, which metabolically releases acetaldehyde, has a MAK value of 200 ml/m$^3$. Therefore, a lower MAK value for the irritant effects of vinyl acetate than that for acetic acid seems implausible.

For vinyl acetate, a NOAEC has been obtained for the mutagenic and clastogenic effects in vitro (Budinsky et al. 2013). The non-linear concentration–response relationship in this study confirmed the non-linear concentration–response relationship for tumours in animal experiments and allows the derivation of a NOAEC for genotoxicity of approximately 50 µM vinyl acetate or acetaldehyde. According to the PBPK model, this NOAEC is not exceeded at an external concentration of 50 ml vinyl acetate/m$^3$ in nasal tissue in rats and, if the PBPK model is followed, at 10 ml/m$^3$ in humans.

**Peak limitation.** Because the critical end point is a local effect, vinyl acetate has been assigned to Peak Limitation Category I. Human studies show that there are minor local effects at 20 ml/m$^3$ and after 4-hour exposure. Therefore, an excursion factor of 1 has been set. Concentrations above 20 ml/m$^3$ lead to more pronounced irritation after 2-hour exposure. In order, as far as possible, to prevent even short-term exposures in this range, a momentary value of 20 ml/m$^3$ has been set, since 2-minute exposures to concentrations of up to 20 ml/m$^3$ caused only marginal irritant effects.

**Prenatal toxicity.** In a developmental toxicity study in rats with inhalation exposure, a decreased mean body weight, a shortened mean crown-rump length and an increased number of skeletal variations, mostly in the form of ossification delays, were observed in the foetuses at the maternally toxic concentration of 1000 ml/m$^3$. After administration in drinking water, developmental and maternal toxicity were not observed in the same species at up to 477 mg/kg body weight and day. No malformations were reported after either inhalation exposure or after application in drinking water. After exposure by inhalation, the NOAEC for developmental and maternal toxicity was 200 ml/m$^3$ and the LOAEC 1000 ml/m$^3$. Taking into account the increased respiratory volume (1:2), this results in a 10-fold and 50-fold margin between the NOAEC and LOAEC for developmental toxicity and the MAK value of 10 ml/m$^3$ for inhalation exposure. The following toxicokinetic data are taken into consideration for the extrapolation of the NOAEL of 477 mg/kg body weight and day after administration in drinking water to a concentration in workplace air: the species-specific toxicokinetic correction value (1:4) for the rat, the assumed oral absorption (100%), the body weight (70 kg) and respiratory volume (10 m$^3$) of the person, and the assumed 100% absorption by inhalation. The concentration calculated from this is 835 mg/m$^3$ air, which is 23 times the MAK value of 10 ml/m$^3$ (36 mg/m$^3$). Also the 2-generation study with administration in drinking water did not reveal perinatal toxicity in the offspring until postnatal day 7 up to the highest dose levels tested during gestation (671 and 648 mg/kg body weight and day for the F0 and F1 dams, respectively). These dose levels, taking into consideration the 7-day treatment of the animals in comparison with the 5 days per week exposure at the workplace, correspond to concentrations in air of 1644 and 1588 mg/m$^3$, respectively, which are 46 and 44 times the MAK value of 10 ml/m$^3$ (36 mg/m$^3$). Due to the sufficient margin between the (calculated) concentration in air and the MAK value of 10 ml/m$^3$, vinyl acetate has been assigned to Pregnancy Risk Group C.

**Germ cell mutagenicity.** In 2002, vinyl acetate was not classified in one of the categories for germ cell mutagens (Greim 2005).

Vinyl acetate causes DNA–protein cross-linking in vitro. This effect is attributed to the metabolite acetaldehyde. In the Salmonella mutagenicity test the substance was not mutagenic. At higher concentrations, test results with vinyl acetate were positive in the micronucleus test, chromosomal aberration test and SCE test in vitro.

New studies demonstrated a non-linear concentration–response curve for mutagenicity and clastogenicity with a NOAEC for micronucleus formation of 50 µM for both vinyl acetate and acetaldehyde. In vivo, micronuclei and SCE were observed in bone marrow cells of mice at very high single intraperitoneal doses, but not after inhalation exposure or after administration of vinyl acetate in drinking water. The results of an in vivo micronucleus test in germ cells (spermatids) were negative.

Vinyl acetate continues not to be classified in one of the categories for germ cell mutagens.

**Absorption through the skin.** For humans, an in vitro study (Section 3.1) estimated the maximum dermal absorption to be 578 mg after exposure to a saturated aqueous solution under standard conditions (2000 cm$^2$ of skin, exposure for 1 hour).

The systemic NOAEC after long-term inhalation exposure of rats is 180 mg/m$^3$. The following toxicokinetic data are taken into consideration for the extrapolation of this concentration as the systemic NOAEL to humans: the respiratory

volume in 8 hours (10 $m^3$), the assumed 100% absorption by inhalation, the extrapolation of data from animal experiments to humans (1:2) and the increased respiratory volume at the workplace (1:2). This results in a systemically tolerable amount of 450 mg.

Absorption through the skin thus makes up more than 25% of the systemically tolerable amount. The substance has therefore been designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

**Sensitization.** There are no findings concerning sensitizing effects of vinyl acetate on the skin or airways in humans and no reliable positive results from experimental studies in animals or in vitro studies. The substance is therefore not designated with "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

# Notes

### Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (www.dfg.de/mak/conflicts_interest) ensure that the content and conclusions of the publication are strictly science-based.

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