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TOXICOLOGICAL EVALUATIONS

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TOXICOLOGICAL EVALUATION

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Vinyl propionate

No. 261

CAS No. 105-38-4

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Vinyl propionate

Note: Vinyl propionate – similarly to the structurally related chemical, vinyl acetate, which in the Federal Republic of Germany has been classified by the hazardous substances committee ("Ausschuss für Gefahrstoffe" (AGS)) and placed in category 3 of carcinogenic compounds (TRGS 905, 2000) – is rapidly hydrolysed by esterases to yield the parent acid and acetaldehyde, an established finding reported in early in-vivo studies in rats and rabbits as well as in in-vitro studies in rat and human blood. In accordance with Annex I to Directive 67/548/EEC, acetaldehyde has also been placed into category 3 of carcinogenic substances.

1 Summary and assessment

According to older studies, vinyl propionate is rapidly cleaved into propionic acid and vinyl alcohol in rabbits and rats in vivo and in rat and human blood in vitro, and vinyl alcohol is then further metabolised to acetaldehyde.

On acute oral and dermal exposure, vinyl propionate is found to be of low toxicity (LD_{50} rat oral approx. 3000, 4365 and 4677 mg/kg body weight; LD_{50} rabbit dermal 9170 mg/kg body weight). A single 3-hour inhalation of 4000 mg vinyl propionate/m³ is tolerated without symptoms by the rat, mouse, cat and rabbit. Higher concentrations cause airway irritation, breathing difficulties, convulsions and death. In mice, the LC_{50} after 2-hour exposure is reported as 6300 mg/m³. On subcutaneous and intraperitoneal administration to mice, LD_{50} values of approx. 2000 and 466 mg/kg body weight, respectively, have been reported. The repeated oral administration of the substance at dose levels of 500 to 2000 mg/kg body weight over a period of 3 to 24 days causes diarrhoea, vomiting, weight loss and death in rabbits and cats. Macroscopic findings in rabbits include gastric mucosal bleeding and, following administration of 2000 mg/kg body weight, histopathologically confirmed inflammation of the small intestine. Seven inhalation exposures to 9000 mg vinyl propionate/m³ caused mucous membrane irritation and breathing difficulties in the cat and dyspnoea, convulsions and death in mice, whereas rabbits and rats tolerated the treatment without symptoms.

The substance has proved to be irritating to the skin of the rabbit. The rabbit eye shows reversible signs of irritation.

Vinyl propionate has no sensitising effect on guinea pig skin.

According to older studies, no macroscopic or histopathological changes were observed following dietary administration of vinyl propionate to female rats for 223 and 392 days. Following 4-month exposure of mice, rats and rabbits to vinyl propionate levels of 1000 mg/m³, the mice were affected in their body weight development, did not swim as long as the controls in swimming tests and exhibited reduced oxygen consumption. The rats and the rabbits had low thyroid and adrenal gland weights compared with the controls. In the rabbits, inhibition of the reflexes was observed. Insufficient documentation of the experimental setup and the results (e.g. details of analytical verification and histopathological findings are lacking) render the studies unsuitable for the assessment of the systemic toxicity of vinyl propionate following repeated inhalation administration.

In the Salmonella/microsome assay, the substance is found to test negative both with and without metabolic activation. By contrast, positive results have been reported for the chromosome aberration test in V79 cells of the Chinese hamster with and without metabolic activation and for the sister chromatid exchange test in human lymphocytes without metabolic activation. On the basis of the available in-vitro data, it appears likely that vinyl propionate has a genotoxic potential.

The threshold concentration producing irritant effects in humans is reported as 400 mg/m³.

2 Name of substance

2.1	Usual name	Vinyl propionate
2.2	IUPAC name	Propionic acid vinyl ester
2.3	CAS No.	105-38-4
2.4	EINECS No.	203-293-5

3 Synonyms, common and trade names

Propanoic acid, ethenyl ester
Propionic acid, vinyl ester
Vinylpropanoate
Vinylpropionat
Vinylpropionate

4 Structural and molecular formulae

4.1 Structural formula

4.2 Molecular formula $C_5H_8O_2$

5 Physical and chemical properties

5.1	Molecular mass, g/mol	100.12	
5.2	Melting point, °C	–80	(EC, 1996; Falbe and Regitz, 1992)
		–81.1	(Lewis, 1995)
5.3	Boiling point, °C	Ca. 95	(EC, 1996; Falbe and Regitz, 1992)
		95	(Lewis, 1995)
		91.2	(Lide and Frederikse, 1996)
5.4	Vapour pressure, hPa	13.3 (at 0 °C)	
		64.5 (at 20 °C)	(Roscher et al., 1983)
		45.8 (at 20 °C)	
		196.3 (at 50 °C)	(EC, 1996; Rinno, 1993)
5.5	Density, g/cm³	0.917 (at 20 °C)	(EC, 1996)
		0.9173 (at 20 °C)	(Lewis, 1995)
5.6	Solubility in water	5.9 g/l (at 25 °C)	(EC, 1996; Rinno, 1993)
5.7	Solubility in organic solvents	Unlimited solubility in alcohol and all usual solvents	(BASF, 1992)
		Soluble in DMSO	(BASF, 1989, 1993)

5.8	Solubility in fat	Unlimited solubility in vegetable oils (BASF, 1992) Partition coefficient n-octanol/water, log P_{ow}: 1.14 (EC, 1996)
5.9	pH value	No information available
5.10	Conversion factor	1 ml/m³ (ppm) ≙ 4.09 mg/m³ 1 mg/m³ ≙ 0.24 ml/m³ (ppm) (at 1013 hPa and 25 °C)

6 Uses

Used as the starting material in the manufacture of homopolymers as well as copolymers in combination with monomers such as (meth-)acrylic compounds, vinyl chloride and other vinyl esters (Roscher et al., 1983).

7 Experimental results

7.1 Toxicokinetics and metabolism

Rabbits (with and without tracheotomy) were exposed to vinyl propionate vapour at concentration levels of approx. 2000 mg/m³. With the aid of a polarographic method (no further details), the concentration of vinyl propionate was measured in the inhaled and the exhaled air after 1 minute, approx. 50 minutes and approx. 90 minutes of exposure as well as in the exhaled air at 1 minute after the end of exposure (after 110 to 170 minutes). During and after exposure, blood was drawn from the left carotid artery and also analysed for vinyl propionate content by means of the polarographic method. Vinyl propionate retention was approx. 45%. An equilibrium between inhaled and exhaled air was reached during the first few minutes of exposure. After the end of exposure, vinyl propionate was no longer detectable in the exhaled air. The animals' blood contained no detectable amounts of vinyl propionate. According to the author, vinyl propionate undergoes rapid metabolism in the lung to yield propionic acid and vinyl alcohol, the latter being further metabolised to acetaldehyde (Filov, 1959).

In the blood of 10 rats which were exposed to vinyl propionate vapour until narcosis occurred, mean acetaldehyde levels of 23.4 µg% (µg/100 ml) we-

re detected, but no vinyl propionate was found (no further details; Filov, 1959).

In-vitro studies have also demonstrated metabolisation to acetaldehyde. Amounts of 0.38 mg vinyl propionate were added to 2 ml rat and human blood and analysed for acetaldehyde content by spectrophotometry at different time points (1 to 20 minutes; no details of the incubation conditions). The amount of acetaldehyde determined in the blood accounted for approx. 90% of the amount of vinyl propionate which had been added. The author attributed the remaining 10% to losses during analysis. Thus, vinyl propionate underwent rapid and complete hydrolysis in vitro as well (Filov, 1959).

7.2 Acute and subacute toxicity

Acute toxicity

- **Oral administration**

Following oral administration of vinyl propionate (10% in peanut oil) at dose levels of 500 to 4000 mg/kg body weight, an LD_{50} value of approx. 3000 mg/kg body weight was determined in white rats. Clinical signs of toxicity seen shortly after administration included swaying gait, lying on the abdomen and “paralysis” of the limbs. Death occurred after 1 to 2 hours (BASF, 1952).

A further LD_{50} value found after oral administration to Carworth-Wistar rats was reported as 4.76 ml/kg body weight (equivalent to 4365 mg/kg body weight). The post-treatment observation period was 14 days (no further details; Smyth et al., 1962).

Upon oral administration to rats of 2% and 20% aqueous emulsions of vinyl propionate in tragacanth gum, the LD_{50} value observed after a 7-day observation period was 5100 (4250 to 6120) µl/kg body weight (equivalent to 4677 (3897 to 5612) mg/kg body weight). Convulsive tremors, apathy and diarrhoea or soft faeces were observed as clinical signs of intoxication. The post-mortem in part revealed gastric ectasia, intestinal atony and/or congestive hyperaemia of the small intestine (BASF, 1967).

• **Dermal application**

In male New Zealand rabbits, dermal application of vinyl propionate for 24 hours gave an LD_{50} value of 10000 µl/kg body weight (equivalent to 9170 mg/kg body weight). The post-treatment observation period was 14 days (no further details; Smyth et al., 1962).

• **Inhalation administration**

At nominal vinyl propionate concentrations of approx. 400, 250 and 110 ppm (equivalent to approx. 1623, 1023 and 450 mg/m³), exposures lasting 26, 23 and 40 minutes, respectively, were lethal to all male albino rats (300 to 450 g, 4 or 5 rats/group) in the study. Shortly after the beginning of exposure hyperpnoea was observed, followed by dyspnoea, apnoea and, ultimately, death from respiratory paralysis. When rats were exposed to approx. 4 ppm (equivalent to approx. 16 mg/m³) for one hour, they developed a respiratory syndrome. Removed to fresh air, the animals recovered promptly and completely. Animals exposed to this same concentration intermittently (6 one-hour exposures with two hours' rest between exposures) were not seriously affected. During exposures, the respiratory syndrome was observed, which was reversible during the resting periods (Ambrose, 1950).

One cat, 1 rabbit, 4 rats and 10 mice each underwent a single exposure to vinyl propionate levels of 110000 mg/m³ (approx. 27000 ppm; duration of experiment 15 minutes), 23000 mg/m³ (approx. 5600 ppm; duration of experiment 3 hours), 9000 mg/m³ (approx. 2200 ppm; duration of experiment 3 hours) and 4000 mg/m³ (approx. 900 ppm; duration of experiment 3 hours). Single inhalation of 110000 mg/m³ was fatal to the cat, the majority of the rats, and the mice within 15 minutes. In the cat, this concentration immediately caused lacrimation and salivation and resulted in lying on the side and convulsions after 3 minutes, death occurring after 5 minutes. The rabbit also displayed a lateral position and convulsions, which were reversible, however, within one hour after the end of exposure. Following exposure, cloudiness of the cornea was noted. After 3 days, the animal died from purulent tracheobronchitis and bronchopneumonia. The rats and mice had severe dyspnoea and all but one rat died in convulsions, lying on their sides. Gross pathology of the cat and the rats was without findings. The cat and the mice which were exposed to 23000 mg/m³ did not survive either.

The signs of intoxication were the same as those seen at the higher concentration. A single 3-hour inhalation of 4000 mg/m³ by the cat and the rabbit caused mucous membrane irritation, while it resulted in dyspnoea, convulsions and death in 3 out of 10 mice. The single 3-hour inhalation of 4000 mg/m³ was tolerated without symptoms by all of the rats. The great discrepancy between the vapour concentrations identified in the two studies as being relatively nontoxic (4000 and 16 mg/m³) could be attributable to a calculation error in the publication by Ambrose (1950; it is suspected that mg/l and ml/m³ were confused; BASF, 1952).

Four-hour exposure to a vinyl propionate concentration of 4000 ppm (equivalent to 16400 mg/m³) was fatal to 4 out of the 6 albino rats (no further details; Smyth et al., 1962).

In the inhalation risk test with atmosphere which was enriched with vinyl propionate vapours at 20 °C, none of the rats subjected to a 3-minute exposure died, whereas 9 out of 12 rats died after a 10-minute exposure. The signs of toxicity included severe mucous membrane irritation, dyspnoea, reeling and light narcosis. Autopsy was without abnormal findings (BASF, 1967).

Male and female white mice (weighing 17 to 21 g; 10 or 20 per group) were exposed to calculated vinyl propionate levels of 2000 to 48000 mg/m³ for 2 hours. At concentration levels of 2000 and 4000 mg/m³ irritation of the upper respiratory tract and increased motility were seen, and at 6000 and 8000 mg/m³ general agitation and dyspnoea, tonic-clonic convulsions and deaths occurred in addition. Exposure to 10000 mg/m³ led to lying on the side after 10 to 12 minutes, while exposure to 16000, 32000 and 48000 mg/m³ resulted in deep narcosis and deaths. Necropsy revealed pulmonary oedema of varying degree. For mice, the LC_{50} was given as 6300 mg/m³ (2 hours), while the threshold concentration for pulmonary oedema was reported as 2000 mg/m³ (2 hours; Golubev, 1957 a, b, d).

- **Parenteral administration**

In white mice, the LD_{50} value observed after subcutaneous administration of vinyl propionate (10% in peanut oil, 500 to 4000 mg/kg body weight) was given as approx. 2000 mg/kg body weight. In the fatally poisoned animals, dyspnoea and signs of paralysis were seen shortly upon injection. Two ani-

mals were observed to be bleeding from the nose and snout. Death occurred between 20 minutes and 2 hours after administration. The survivors showed no obvious signs of intoxication (BASF, 1952).

Following intraperitoneal administration of vinyl propionate (2% and 20% aqueous tragacanth emulsions) to mice, the LD_{50} was determined as 508 (141 to 622) µl/kg body weight (equivalent to 466 (129 to 570) mg/kg body weight). The clinical signs of toxicity included reeling, lying on the abdomen and forced respiration. Necropsy revealed adhesions in the abdominal cavity, diarrhoea and intestinal atony (BASF, 1967).

Subacute toxicity

In one rabbit, oral administration of daily vinyl propionate doses of 2000 mg/kg body weight (20% in peanut oil) for 3 days caused diarrhoea, weight loss and death following the third dose. After the second dosing by gavage, the urinary protein and reduction tests were positive. The sediment contained fragments of urinary casts and some leukocytes. At necropsy, the gastric mucosa was found to be extensively permeated with blood and there was reddening of the upper portion of the appendix. Histopathological examination revealed inflammation of the small intestine. In a further rabbit, daily administration of 1000 mg/kg body weight by oral gavage for 4 days also resulted in diarrhoea, weight loss and death following the fourth dose. At autopsy, no macroscopic or histopathological changes were evident apart from localised gastric mucosal bleeding. Administration of 24 oral doses of 500 mg/kg body weight within a period of 30 days to another rabbit resulted in a slight reduction in haemoglobin levels and erythrocyte counts, and in weight loss. The animal died after the 24th dose. Necropsy revealed bronchopneumonia and gastric mucosal bleeding (BASF, 1952).

In one cat, 10 oral vinyl propionate doses of 1000 mg/kg body weight, administered over a period of 12 days, caused weight loss, slight disturbances of balance and occasional vomiting. The blood count was normal. The urine contained protein (on two occasions) and the reduction test was positive (on one occasion). At autopsy, no pathological changes were evident. On receiving 38 oral doses of 1000 mg/kg body weight over a period of 52 days, another cat repeatedly exhibited vomiting, loss of appetite, apathy, drowsiness, weight loss and diarrhoea. The urine repeatedly contained

protein but was normal at the end of the study. The autopsy findings were described as fatty degeneration of the liver. Histological examination did not reveal any clear-cut pathological changes (BASF, 1952).

Seven 4-hour inhalation exposures to vinyl propionate at 9000 mg/m³ (approx. 2220 ppm) given over a period of 9 days caused mucous membrane irritation and transient breathing difficulties in one cat, while in mice (10 animals), dyspnoea, convulsions, lying on the side and 3 deaths resulted during the first inhalation. One rabbit and 4 rats showed no signs of intoxication. Urine and blood count were normal in the cat and the rabbit. The rabbit had no liver dysfunction (BASF, 1952).

7.3 Skin and mucous membrane effects

Skin irritation studies

Application of 0.02 and 0.04 ml vinyl propionate to the abraded and unabraded skin of 9 rats every 5 minutes for one hour each day for 4 to 6 days produced only a slight skin reaction, which cleared up within 2 days after the last application (Ambrose, 1950).

In rabbits, no serious local or systemic effects were observed after application of vinyl propionate to the skin. On repeated daily application for 7 days, a progressive deterioration of the skin at the point of application was observed in 3 animals (no indication of the total number). The skin appeared leathery. Within 5 days after the last application, the leathery integument sloughed off and was replaced by normal tissue (Ambrose, 1950).

When applied to the dorsal skin of white rabbits for 20 hours, undiluted vinyl propionate and a 50% solution of the chemical in peanut oil produced reddening of the skin with subsequent desquamation in 2 out of 2 and in 2 out of 4 animals, respectively. A 10% solution in peanut oil was not irritating (BASF, 1952). Therefore, the chemical was irritating to the skin.

Undiluted vinyl propionate caused oedema and slight reddening when the dorsal skin of rabbits was exposed to the chemical for 1 to 15 minutes. After 8 days, mild to heavy desquamation were noted, and 15-minute exposure was observed to produce severe reddening and mild oedema in addition. Following 20-hour exposure, severe reddening and severe oedema

occurred. Examination after 8 days revealed heavy desquamation (BASF, 1967). Vinyl propionate thus proved to be irritating to the skin.

When applied to the rabbit ear for 20 hours (one rabbit per test), undiluted vinyl propionate and a 50% solution in olive oil produced severe inflammation which was associated with necrosis and formation of partly suppurating blisters. A 10% solution in olive oil also caused severe irritation which was accompanied by the formation of oedema and blisters, which healed up only slowly (BASF, 1952).

After a 20-hour application of undiluted vinyl propionate to the inner side of the rabbit ear, severe reddening and oedema, partly anaemic-necrotic, were observed. After 8 days, severely weeping necrosis and cutaneous haemorrhages were noted (BASF, 1967).

On the basis of the results described above (BASF, 1952, 1967), vinyl propionate was evaluated as irritating to the skin (EC, 1996).

A 24-hour uncovered application of 0.01 ml vinyl propionate to the shorn abdominal skin of 5 albino rabbits produced irritant effects of grade 2 on an ascending 10-point irritancy scale (no further details; Smyth et al., 1962).

In rats, intracutaneous injection of 0.1 ml vinyl propionate produced a slight degree of necrosis and scarring, which healed within two days (Ambrose, 1950). The reported findings seem implausible.

Studies on mucous membrane effects

Instilled into the conjunctival sac of rabbits, 0.1 ml of a 10% solution of vinyl propionate in propylene glycol caused slight chemosis and conjunctivitis, both persisting for about 24 hours. Upon instillation of 0.1 ml undiluted substance, extensive chemosis and conjunctivitis were observed. Seven days after treatment, the eyes appeared normal again (Ambrose, 1950).

Applied to the rabbit eye, undiluted vinyl propionate caused purulent inflammation which persisted for several days, whereas a 10% solution in olive oil resulted in mild irritation which was reversible after 24 hours (BASF, 1952).

Instillation of one drop of undiluted vinyl propionate into the rabbit eye produced slight reddening and severe oedema after one hour as well as ques-

tionable cloudiness of the cornea after 24 hours. When 2 drops were instilled at an interval of 5 minutes, severe reddening, severe oedema and slight cloudiness of the cornea resulted after one hour. After 24 hours, questionable reddening was still observed. The findings cleared up after 8 days. One drop of a 10% solution in olive oil led to slight reddening after one hour, which was reversible after 24 hours (BASF, 1967).

On the basis of the results described above (BASF, 1952, 1967), vinyl propionate was evaluated as not irritating to the eye (EC, 1996).

The instillation of vinyl propionate into the rabbit eye produced irritant effects of grade 2 on an ascending 10-point irritancy scale (no further details; Smyth et al., 1962).

Following 30-minute exposures of 3 cats to vinyl propionate at levels of 1000, 2000, 3000, 4000 and 6000 mg/m³, irritation of the eyes and upper respiratory tract were noted. Upon inhalation by rabbits, irritation of the airways was observed in the form of altered breathing frequency (Golubev, 1957 b).

When applied onto the penile mucosa of rabbits, 0.2 ml vinyl propionate (10% in propylene glycol) caused slight hyperaemia and oedema. The oedema was still present after 24 hours. Application of 0.2 ml undiluted substance resulted in extensive oedema which lasted for about 3 days. After 7 days, the findings cleared up (Ambrose, 1950).

7.4 Sensitisation

Vinyl propionate (99.8% pure) was studied in the Magnusson and Kligman maximisation test with respect to its sensitising potential in the guinea pig (OECD guideline No. 406). For intradermal induction, 20 female Pirbright-White Dunkin-Hartley guinea pigs (initial weight 321 to 397 g) were treated with a 5% formulation of the test substance in olive oil, whereas dermal induction was carried out with undiluted test substance. Ten other animals served as controls. Dermal challenge followed 14 days after dermal induction and was performed with a 75% solution of the test substance in olive oil. Neither the test group nor the control group showed skin reactions when examined 24 and 48 hours after removal of the patches. Vinyl propionate thus proved not to have a sensitising effect on guinea pig skin (BASF, 1997).

7.5 Subchronic and chronic toxicity

Groups of 5 female albino rats (weighing approx. 41 g at the beginning of the study) were given vinyl propionate in their feed at concentration levels of 0.005, 0.01, 0.02, 0.04, 0.08, 0.16, 0.32, 1.28 and 2.56% for 223 days, and at a level of 0.64% for 392 days. Based on a food consumption of approx. 50 g/kg body weight, the ingested daily doses were equivalent to approx. 2.5, 5, 10, 20, 40, 80, 160, 320 and 640 mg/kg body weight, and 1280 mg/kg body weight, respectively. A control group of 5 animals was included. Body weight and food consumption were determined on a weekly basis. At study termination, gross and histopathological examination of the thyroid gland, heart, lungs, liver, kidneys, adrenal glands, intestine, stomach, pancreas, urinary bladder and reproductive organs was performed. At the highest concentration level, body weight development was slightly inhibited and food consumption was about 1 g/day lower than in the other groups, an observation which the author considered to be attributable to the very low values seen in one animal. The macroscopic and histopathological findings were negative in all groups (Ambrose, 1950).

Groups of 50 mice, 10 rats and 5 rabbits (strain and sex not specified) were exposed to a vinyl propionate vapour concentration of 1000 mg/m³ for 6 hours/day over a period of 4 months. The same numbers of animals served as controls. In the rats and rabbits, body weight development during the study was not affected, while in the mice it was reduced relative to controls. In swimming tests in warm water of 38 to 39 °C, the exposed mice swam for markedly shorter periods of time than did the controls (exposed mice 96.4 minutes, controls 134.5 minutes), a reduction in performance which the author attributed to exposure. After the end of exposure, oxygen consumption was determined in the mice and the rats. It was found to be 92.8 ml/hour/20 g and 101.7 ml/hour/20 g in the exposed mice and the controls, respectively. Similar results were also obtained for the rats (no further details). In the rabbits, haemoglobin content as well as erythrocyte and leukocyte counts were determined before and during exposure. There were no changes in haemoglobin content and erythrocyte count, whereas leukocytosis of a lymphocytic type in association with marked monocytosis was noted even at the beginning of exposure. When the flexor reflex was tested in the rabbits, inhibition of the reflexes became apparent. Compared with controls, there were no changes in the rabbits as regards body temperature measurements and thoracic x-rays, and in the rats urinalyses were un-

changed. The rats and rabbits had lower absolute thyroid and adrenal gland weights than the controls. No histopathological examinations were carried out. On the basis of the results from this study and the acute toxicity studies conducted by the investigator (Golubev, 1957 a, b, d), 30 mg/m³ was recommended as the maximum allowable workplace concentration in the former USSR (Golubev, 1957 c). Insufficient documentation of the experimental setup and the results (e.g. no details are given of analytical verification of test substance concentrations in the atmosphere or of histopathological findings) render the studies unsuitable for the assessment of the systemic toxicity of vinyl propionate following repeated inhalation administration.

7.6 Genotoxicity

7.6.1 In vitro

Vinyl propionate (purity 99.9%, dissolved in DMSO) was tested at concentration levels of 20 to 5000 µg/plate for mutagenicity in the Salmonella/microsome assay (standard-plate incorporation test and preincubation test) using *Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 with and without metabolic activation (S9 mix from Aroclor 1254-induced livers of male Sprague-Dawley rats). No bacteriotoxic effect was observed. Neither in the absence nor in the presence of metabolic activation was any increase in revertant counts seen in the standard-plate test or the preincubation test. The substance thus proved to be devoid of gene mutagenic activity under these experimental conditions (BASF, 1989).

With respect to the induction of chromosome aberrations, vinyl propionate (99.9% pure, dissolved in DMSO) was tested in V79 cells of the Chinese hamster (OECD guideline No. 473) at concentration levels of 250, 500 and 1000 µg/ml with and without metabolic activation (S9 mix from Aroclor 1254-induced livers of male Sprague-Dawley rats). Preparation of the cells was carried out after 18 hours. Chromosome aberrations were evaluated only at the highest test concentration. Both in the absence and presence of metabolic activation, a significant increase was noted in the number of chromosome aberrations (without S9 mix 12%, solvent controls 4.5%; with S9 mix 66%, solvent controls 5.5%). The test substance thus proved clastogenic both in the absence and presence of metabolic activation in this test system (BASF, 1993).

Vinyl propionate (purity unspecified, solvent acetone), when tested in the sister chromatid exchange (SCE) test in human lymphocytes isolated from the blood of a 34-year-old healthy male donor, induced a statistically significant dose-dependent increase in the number of SCEs/cell following a 48-hour incubation period at concentration levels of 0.125 to 0.5 mM (equivalent to 12.5 to 50 µg/ml) without metabolic activation. Concentration levels of and above 1 mM (100 µg/ml) proved to be cytotoxic (Sipi et al., 1992). Therefore, vinyl propionate was found to cause DNA damage in this test system.

7.6.2 In vivo

No information available.

7.7 Carcinogenicity

No information available.

Acetaldehyde, a product of vinyl propionate hydrolysis, has been investigated in a carcinogenicity study with inhalation exposure of male and female Wistar rats (105 males and 105 females/group). The following description of the study was taken from the section on acetaldehyde in “Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten” (Greim, 2000), which provides the toxicological and occupational medical justification for the MAK value and the classifications established for acetaldehyde by the MAK Commission. The daily exposures lasted 6 hours and were carried out 5 days/week over a period of 27 months. Exposure levels were 0 (controls), 750 ppm (1373 mg/m³), 1500 ppm (2747 mg/m³) and in the high-exposure group initially 3000 ppm (5493 mg/m³), the latter concentration being reduced to 1000 ppm (1831 mg/m³) in the course of the study owing to the occurrence of severe growth retardation, transient weight loss and premature deaths. Concentration-dependent effects observed included increased mortality in all dose groups as well as growth retardation in the mid and top dose groups. Treatment-related histopathological changes were confined to the respiratory tract. At all concentration levels, signs of olfactory epithelial degeneration associated with hyperplasia and metaplasia were observed. Hyperplasia and metaplasia of the respiratory epithelium occurred at the mid and high concentrations. The treatment induced two types of

malignant tumour, adenocarcinoma of the olfactory epithelium and squamous epithelial carcinoma of the respiratory epithelium. The incidences of tumours are shown in Table 1.

Table 1. Tumours of the nasal cavity in Wistar rats following 27-month exposure to acetaldehyde

	Males				Females			
Acetaldehyde, ppm	0	750	1500	3000**	0	750	1500	3000**
Number of animals	49	52	53	49	50	48	53	53
Papillomas	0	0	0	0	0	1	0	0
Adenocarcinomas	0	16*	30*	20*	0	6*	26*	20*
–, metastatic	0	0	1	1	0	0	0	1
Carcinoma in situ	0	0	0	1	0	0	3	5
Squamous epithelial carcinoma	1	1	10*	14*	0	0	5	17*
–, metastatic	0	0	0	1	0	0	0	0

* $p < 0.01$ (Fisher's Exact Test)
** initial concentration which had to be reduced in the course of the study

Whereas adenocarcinomas were observed at all acetaldehyde concentrations tested, a higher incidence of squamous epithelial carcinomas occurred only at and above 1500 ppm. Furthermore, histological signs of irritation were seen in the laryngeal region in most animals of the mid and top level groups. The authors summarised their findings concluding that acetaldehyde has a strong cytotoxic effect on the nasal mucosa of rats, with the olfactory epithelium showing a more sensitive reaction than the respiratory epithelium. In addition, the authors pointed out the existing parallels between formaldehyde and acetaldehyde. In both cases, it appears that chronic tissue damage which is caused by irritation and subsequent repair processes plays an important role in the formation of the tumours (Woutersen et al., 1985). Possibly, the carcinogenic effect of acetaldehyde is enhanced in the presence of propionic acid, the second product of hydrolysis, which may act as an additional proliferative stimulus.

7.8 Reproductive toxicity

No information available.

7.9 Effects on the immune system

No information available.

7.10 Neurotoxicity

On exposure of rabbits to vinyl propionate vapours (no details of the concentrations tested), there were changes in natural and conditioned reflexes. Threshold concentrations of 1000 and 200 mg/m³ were given (no further details; Golubev, 1957 b).

7.11 Other effects

No information available.

8 Experience in humans

Ten volunteers (6 men, 4 women) inhaled different concentrations of vinyl propionate via a rubber mask for one minute. The volunteers' subjective impressions were recorded to assess the intensity of the irritating effect on the eyes and respiratory tract. The majority of the subjects complained of dyspnoea and anxiety which occurred about 20 to 30 seconds after the beginning of exposure. A threshold concentration of 400 mg/m³ was given (no further details; Golubev, 1957 b, d).

From the 1989–1994 period, one case of accidental inhalation exposure to vinyl propionate is reported in which the individual was hospitalised for treatment of conjunctival irritation (BASF, 1994).

In the USA, vinyl propionate was detected by gas chromatography and mass spectrometry in 3 out of 8 investigated samples of mother's milk (EPA, 1980).

9 Classifications and threshold limit values

No information available.

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