Workplace Exposure Standard (WES) review

VINYL ACETATE
(CAS NO: 108-05-4)

March 2020

New Zealand Government

WORKSAFE
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1.0
Introduction

This WorkSafe New Zealand (WorkSafe) review considers whether the **WES** for vinyl acetate should be changed.

It considers the potential for exposures to vinyl acetate in New Zealand, the health effects and risks, exposure standards from other jurisdictions around the world, and the practicability of measuring exposures.

The review includes a recommendation to change the WorkSafe WES for vinyl acetate, which is currently set at a **WES-TWA** of 10ppm [35**mg/m^3**] and a **WES-STEL** of 20ppm [70mg/m^3] as published in the special guide *Workplace Exposure Standards and Biological Exposure Indices*, 11th Ed., November 2019 (WorkSafe, 2019).

Terms that are **bold** (first occurrence only) are further defined in the Glossary. Synonyms: Acetic acid ethenyl ester, Acetic acid vinyl ester; Vinyl A monomer; 1-Acetoxyethylene; Ethenyl acetate; VA.

2.0 Chemical and physical properties

Vinyl acetate is a colourless, volatile, flammable liquid at room temperature with an odour described as either sweet and ether-like, or sharp and sour (**ACGIH**®, 2018; **SCOEL**, 2005).

Vinyl acetate usually contains a polymerisation inhibitor [for example, hydroquinone] for storage, otherwise when exposed to light it will polymerise to a transparent colourless mass (ACGIH®, 2018; SCOEL, 2005).

Odour thresholds for vinyl acetate have been reported between 0.36-0.5ppm (ACGIH®, 2018; SCOEL, 2005).

Chemical and physical properties of vinyl acetate include:

Molecular weight	86.09g/mol
Formula; structure	$C_4H_6O_2$
Specific gravity/density	0.9317g/m³ at 20°C
Melting point	-93.2°C
Boiling point	72.3°C at 760 torr
Vapour pressure	120hPa at 20°C; 115 torr at 25°C
Vapour density	3 [air = 1]
Saturated vapour concentration	530,000mg/m³ at 25°C
Flash point	Closed cup: -8°C; Open cup: 1.1°C
Flammable limits	Upper: 13.4%; Lower: 2.6% by volume in air
Autoignition temperature	385°C; 426.6°C
Log K_{ow}	0.73
Solubility	Slightly soluble in water [20g/L at 20°C]; soluble in diethyl ether, acetone, benzene, ethanol, chloroform, and most organic solvents
Reactivity	May polymerise violently; highly flammable; vapours form explosive mixtures with air
Conversion factors	1mg/m³ = 0.28ppm 1ppm = 3.52mg/m³

ACGIH®, 2018; ECHA RAR, 2008; SCOEL, 2005

TABLE 1: Physicochemical properties of vinyl acetate

Health-related hazard classifications for vinyl acetate:

	HSNO CLASSIFICATION
Substance	Acetic acid ethenyl ester
CAS No.	108-05-4
Classification	6.1C (All); 6.1C (I); 6.1D (O); 6.1D (D); 6.3A; 6.4A; 6.6A; 6.7B; 6.8B; 6.9B (All); 6.9B (I)

TABLE 2:
HSNO health–related hazard classifications of acetic acid ethenyl ester (**EPA**, 2019)

For a full listing of all HSNO health-related hazardous substances classification codes and their descriptions, see Appendix 2.

[All] Overall classification for that endpoint.
[O] Oral exposure route.
[D] Dermal exposure route.
[I] Inhalation exposure route.

3.0
Uses

Vinyl acetate is a high-volume production chemical used to produce polyvinyl acetate emulsions, acrylic fibres, and, polyvinyl alcohol (ACGIH®, 2018).

The primary use of the emulsion polymers is in adhesives, paints, printing inks, textiles, and paper products (ACGIH®, 2018; SCOEL, 2005). Copolymers have been used in vinyl floor tiles, textile finishing agents and a wide range of other products (ACGIH®, 2018; **NICNAS**, 2016; ECHA RAR, 2008; SCOEL, 2005).

Vinyl acetate monomer residues can occur in homo- and copolymers based on vinyl acetate and in products/formulations based on these polymers, and the content of residual vinyl acetate monomer in homo- and copolymers depends on the product and the field of application. (ECHA RAR, 2008).

Occupational exposure to vinyl acetate can occur during production, storage, transportation and end-use.

Workers can be exposed to vinyl acetate vapour and liquid via inhalation and eye or dermal contact (ACGIH®, 2018; ECHA RAR, 2008).

The number of workers exposed or potentially exposed to vinyl acetate in New Zealand workplaces is unknown.

Statistics New Zealand 2019 data indicate that 12,970 New Zealand workers were working in the areas of:

- textile finishing and other textile product manufacturing
- basic organic chemical manufacturing
- basic polymer manufacturing
- polymer product manufacturing (NZ.Stat, 2019).

4.0
Health effects

IN THIS SECTION:

4.1 Non-cancer

Humans

The ECHA RAR review of vinyl acetate noted there was no data on the acute toxicity of vinyl acetate to exposed humans (ECHA RAR, 2008).

The **NICNAS** review of acetic acid ethenyl ester summarised the irritation/corrosion potential in exposed humans:

> "The chemical can cause irritation to the nose and throat following exposure via the inhalation route (**ATSDR**, 1992). Respiratory irritation was reported in volunteers exposed to the chemical at 19.4–71ppm for 0.5–4 hours (ACGIH, 2001).
>
> "In workers exposed to the chemical at average levels of 5–10ppm (with possible acute exposures of 300ppm), irritation of the throat and eyes was reported at levels of 21ppm, but eye irritation was not reported under 10ppm (ACGIH, 2001)." (References cited in NICNAS, 2016).

The ACGIH® review of vinyl acetate noted:

> "Exposure to 1.3ppm **VA** for 2 minutes was not irritating to the nose, throat or eyes of 9 volunteers. Irritation of the throat was reported by 1 out of 9 volunteers at 4ppm for 2 minutes, by all 4 subjects exposed to 72ppm for 30 minutes, and 1 out of 3 subjects exposed to 20ppm for 4 hours. Exposure to 20ppm VA for 4 hours, 34ppm for 2 hours, and 72ppm for 30 minutes resulted in olfactory fatigue (Smyth and Carpenter, 1973 as cited in U.S. ATSDR, 1992)." (ACGIH®, 2018).

The ECHA RAR review of vinyl acetate summarised the sensitisation potential in exposed humans:

> "No allergic reactions were observed in twenty-one chemical operators who worked in vinyl acetate production for a mean period of more than 15 years: These operators, evaluated for overall health, were presumably exposed to levels of vinyl acetate in the air in concentrations of approximately 5–10ppm for the duration of their service. In workers which came into contact with vinyl acetate (average exposure to 17.6–65mg/m^3 over 15.2 years, with intermittent exposures near 180mg/m^3) no allergic reactions were observed. However, no patch test was performed (Deese and Joyner, 1969).
>
> "In workers with frequent and intensive dermal exposure to vinyl acetate, no allergic skin reactions could be detected. However, no patch test was performed (Wacker-Chemie, 1995a, Klaschka and Vossmann, 1994).
>
> "Vinyl acetate is not included in standard patch test kits and this may be the reason that data on patch testing with this substance are not available. Thus, the inconclusive or negative data as cited above cannot be used as evidence that vinyl acetate may not cause sensitization by skin contact.
>
> "There is no information available on the potential for vinyl acetate to produce respiratory sensitization in humans." (References cited in ECHA RAR, 2008).

The ECHA RAR review of vinyl acetate summarised the repeated dose toxicity in exposed workers:

> "Information on repeated human exposure to vinyl acetate is small. Quantitative data on exposure and effects were not well investigated or documented. Workers had also been exposed to other compounds, so that effects cannot be attributed clearly to vinyl acetate. Confounding factors (that is, smoking habits) were not ruled out. Therefore the relevance of the observed effects to evaluate risks to human health is questionable."
>
> "A retrospective study on 21 chemical operators in a production plant with mean age of 45.3 years and mean exposure time of 15.2 years to vinyl acetate vapour with concentrations up to 49.3ppm (TWA 5.2–8.2ppm) revealed no vinyl acetate-related injury or differences in medical and biochemical parameters. Local irritant reactions were attributed to occasionally high acute exposures (Deese and Joyner, 1969)." (Reference cited in ECHA RAR, 2008).

The ECHA RAR review of vinyl acetate noted:

> "27 workers in the polyvinyl acetate production were analysed with respect to their frequencies of peripheral lymphocytes with chromosomal aberrations (Shirinian and Arutyunyan, 1980). No exposure data were given. Aberration frequencies varied from 2.2% (1976) to 2.5% (1977) and 2.4% (1978). In a negative control group of 20 workers from the non-chemical industry the aberration frequency was 1.0% in 1978 (not analysed in 1976 and 1977). The negative control group was not 'matched', confounding factors were not considered. The authors do not claim a 'positive' result and no clear conclusion can be drawn." (References cited in ECHA RAR, 2008).

Animals

The ECHA RAR review of vinyl acetate summarised the acute toxicity potential in experimental animals:

> "In tests with rats **LD_{50}** values were in two studies 3470mg/kg and 3500mg/kg, respectively. A dermal LD_{50} value of 7440mg/kg was determined from a range finding study with rabbits. Thus, vinyl acetate needs no labelling according to **EU** criteria with respect to acute oral and acute dermal toxicity. Inhalation toxicity testing, however, resulted in LC50 values of 15.8mg/l/4 hours and 14.1mg/l/4 hours in rats" (Reference cited ECHA RAR, 2008).
>
> "Vinyl acetate exhibits low acute toxicity by the oral and the dermal way of exposure but significant acute inhalation toxicity.
>
> "An oral LD_{50} value of 3.73ml/kg (= 3470mg/kg) was determined in a range finding study in rats.
>
> "The same oral LD_{50} value of 3.76ml/kg (approximately 3500mg/kg) for rats resulted from a study using 2% and 20% vinyl acetate emulsions with traganth.
>
> "A range finding study with rabbits demonstrated a dermal LD_{50} value of 8.0ml/kg (= 7440mg/kg).
>
> "An acute inhalation range finding study with rats resulted in an **LC_{50}** value of 4490ppm (= 15.8mg/l/4 hours)." (Reference cited ECHA RAR, 2008).

The New Zealand EPA classifies vinyl acetate as a 6.1C (I) substance – a substance that is acutely toxic via inhalation and as a 6.1D substance– a substance that is acutely toxic via oral and dermal exposure (EPA, 2019).

The NICNAS review of acetic acid ethenyl ester summarised the irritation/ corrosion potential in experimental animals:

Respiratory irritation

"In an inhalation exposure study, male Sprague Dawley (SD) rats were exposed to the chemical on either one, five or 20 occasions (for six hours per day, five days per week) at doses of 0, 50, 200, 600 or 1000ppm as a vapour via whole body exposure. No clinical signs of toxicity were reported. No treatment-related findings were recorded at gross necropsy. There was a dose related increase in the severity of microscopic lesions in the olfactory epithelium of rats receiving doses of 600ppm and above. Following a single exposure, degeneration, necrosis and exfoliation of olfactory epithelial cells were observed (**REACH**).

"In three-month inhalation studies conducted in rats and mice, clinical signs of toxicity included intermittent symptoms of respiratory distress, hunched posture and ruffled fur. Increased lung weight observed in high dose animals (rats and mice) was attributed to lung congestion arising from respiratory irritation. Treatment-related lesions were observed in the lungs, trachea and nasal epithelium of high dose mice at necropsy (REACH).

"In a four week repeat dose inhalation studies [sic] in rats and mice, clinical signs of toxicity included intermittent symptoms of respiratory distress (REACH)."

"Additional supporting information for respiratory irritation include the necropsy results from an acute inhalation study in rats that showed congested lungs at the mid dose of 4000ppm and haemorrhagic lungs and white froth in the trachea at the high dose of 8000ppm. Also, in a developmental study (via inhalational exposure) in rats, lung congestion in dams was reported (REACH)."

Skin irritation

"In a study conducted with three rabbits (**OECD** Test Guideline (**TG**) 404), the chemical (0.5mL undiluted) caused slight irritation in two animals at the 24-hour observation. Signs of irritation persisted in one animal at the 48-hour observation, and no irritant effects were recorded at the 72-hour observation (individual mean scores were 0.67, 0.33 and 0 for erythema and zero for oedema in all animals) (REACH). The chemical may cause slight skin irritation.

"Six rabbits exposed to the chemical (0.5mL undiluted) for four hours (non-guideline study) showed stained skin which did not allow scoring for erythema. Each rabbit had two test sites, one intact site and one abraded site. Staining affected 4/6 rabbits at the 24-hour observation, with 1/6 rabbits still affected at the 72-hour observation. A subdural haemorrhage was observed in 1/6 rabbits at the 72-hour observation. The chemical was reported as not corrosive (REACH).

"In another (non-guideline) study, five rabbits exposed to 0.01mL of undiluted chemical on clipped intact skin for 24 hours showed no irritation effects (REACH)."

Eye irritation

"In a study conducted with three rabbits (OECD TG 405), slight irritation effects were observed at one and 24 hours after instillation of the chemical (0.1mL undiluted). The mean individual score (24, 48 and 72 hours) for conjunctival redness for each animal was 0.33. There were no corneal or iridial effects observed. No irritation was observed at the 48-hour observation (REACH).

"Following a single instillation of the chemical (0.5mL undiluted) into the eye, corneal injury was assessed in five rabbits on a scale of 1–10. Corneal injury was present in four out of five rabbits (described as either trace or minor injury). Eye irritation was scored as two on the scale (1–10). The chemical was determined to be slightly irritating to the eyes (REACH)." (References cited in NICNAS, 2016).

The New Zealand EPA classifies vinyl acetate as a 6.3A and 6.4A substance – a substance that is irritating to the skin and irritating to the eye respectively (EPA, 2019).

The NICNAS review of acetic acid ethenyl ester summarised the sensitisation potential in experimental animals:

"In an OECD TG 429 compliant **LLNA** using CBA/CaOlaHsd mice, the chemical was determined not to be a skin sensitiser. The stimulation index (**SI**) values for the chemical at the tested concentrations were 2 (5% concentration), 2.4 (10%), 1.9 (25%), 1.7 (50%), and 1.3 (100%). Signs of skin irritation were not observed during the irritation screen; however, slight to moderate ear swelling was observed during the main test which may indicate increased potential for skin irritation caused by the chemical with repeated dosing (REACH).

"Some skin sensitisation potential was reported in a study using methodology similar to OECD TG 406 (Buehler assay method; except with nine induction doses using the undiluted chemical), where the chemical tested positive (minimum positive response of 15%; only 3/20 animals showed a sustained response over 48h at challenge) for skin sensitisation in Hartley guinea pigs following challenge with the chemical at a concentration of 25% in acetone (REACH).

"The methodology used in this study (that is, nine inductions) would likely maximise any potential for sensitisation of the chemical compared with the Buehler protocol but only resulted in the minimum positive response level for the Buehler protocol. The LLNA result is considered to be the more reliable indicator of the skin sensitisation potential of the chemical." (References cited in NICNAS, 2016).

The ECHA RAR review of vinyl acetate noted:

"Overall, the outcome of both studies may indicate that vinyl acetate is not devoid of a skin sensitising potential. The results of the LLNA do confirm the weak-moderate effects seen in the Buehler test. However, since the positive threshold level was not exceeded in the LLNA, classification and labelling with R 43 is not warranted. The LLNA was given a higher reliability since pure vinyl acetate was used for testing whereas a commercial grade test substance was applied in the Buehler test. In addition, the Buehler test was not fully compliant to the EU testing guideline due to some deviations of the test protocol." (ECHA RAR, 2008).

The ECHA REACH Dossier for vinyl acetate summarised the repeated dose inhalation toxicity in experimental animals:

"For whole-body inhalation exposure of vinyl acetate, the key study was a combined repeated dose and carcinogenicity study using rats and mice. The study was conducted and reported (Hazleton, 1988b) and some details published subsequently (Bogdanffy *et al*, 1994b). The study was **GLP** compliant, conducted to current testing guidelines and therefore considered to represent the most reliable data for risk characterisation. Supporting studies include the preceding 4-week sighting studies (Hazleton 1979a; 1979b) and 90 day studies (Hazleton 1980d; 1980e) in rats and mice. An investigative study was conducted to evaluate nasal epithelial cell proliferation in male rats (Bogdanffy *et al*., 1997).

"The key combined repeated dose and carcinogenic study exposed rats and mice to vinyl acetate vapour at concentrations of 0, 50, 200 or 600ppm (6 hours/day, 5 days/week) over a period of 2 years (Hazleton, 1988b). The study also included satellite groups for interim evaluation at week 53, interim evaluation at week 83 and, post-recovery evaluation (70 weeks exposure/ 15/16 weeks recovery). A reduction in body weight gain was observed for rats and for mice exposed to 600ppm and for mice exposed to 200ppm. Thus the **NOAEC** for systemic toxicity was 200ppm for rats (704mg/m^3) and 50ppm for mice (176mg/m^3). For both species, local effects of vinyl acetate exposure were confined to the respiratory system. Morphological non-neoplastic lesions were observed in the nasal cavity of rats and mice exposed to 200 or 600ppm, in the trachea of mice exposed to 200 or 600ppm and, in the lungs of the rats and mice exposed to 600ppm. Thus the NOAEC for local toxicity was 50ppm (176mg/m^3).

"Two supporting studies exposed rats and mice to vinyl acetate vapour at concentrations of 0, 50, 200 or 1000ppm (6 hours/day, 5 days/week) for 90 days (Hazleton 1980d; 1980e). Although the quality of the rat study may have been affected by parasitic infection (indicated by eosinophilic gastritis and colon nematodiasis in most control and high dose animals), exposure to 1000ppm vinyl acetate resulted in lower body weight gain, intermittent clinical signs including respiratory distress, hunched posture and ruffled fur, increased lung weight and mild histomorphological changes in the respiratory tract. The NOAEC for local and systemic effects was 200ppm (704mg/m^3). For mice exposed to 1000ppm, clinical signs included ruffled fur, hunched posture and respiratory distress and body weight gain was reduced; histomorphological changes were seen in the respiratory tract. Respiratory distress and hunched posture were observed during the first 9 days of exposure to 200ppm in the absence of any effect of vinyl acetate on body weight gain. The NOAEC for local and systemic effects was 50ppm (176mg/m^3).

"These two 90 day studies were preceded by 4-week sighting studies in which rats and mice were exposed to 0, 50, 150, 500 or 1000ppm of vinyl acetate vapour (6 hours/day, 5 days/week) (Hazleton 1979a; 1979b). The exposure concentration of the 50ppm group was increased to 1500ppm on exposure day 8 (mice) or on exposure day 10 (rats). Mice exposed to 150ppm or more and rats exposed to 500ppm or more showed transient signs of hunched posture and respiratory distress which were dose-related. There was no clear effect of vinyl acetate on body weight. Histopathological examination revealed hyperplastic and metaplastic change in the epithelium of the respiratory tract of mice. The NOAEC for systemic effects was 1500ppm in rats and mice and the NOAEC for local effects was 50ppm in mice (176mg/m^3) and 150ppm in rats (528mg/m^3). The relatively high NOAEC value for systemic effects may be a consequence of the limited test parameters of this range-finding study and reduces the reliability of the value.

"An investigative study evaluated the effects of vinyl acetate exposure on nasal epithelial cell proliferation in male rats exposed for 1, 5 or 20 days (6 hours/day, 5 days/week) to 0, 50, 200, 600 or 1000ppm (Bogdanffy, Gladnick *et al*.,1997). Cell proliferation was assessed by histopathological evaluation of 5 cross sections of the nose and by immunocytochemistry (level of **BrdU** incorporation following BrdU injection 16 hours after the last exposure). No treatment-related difference in the labelling index of the respiratory epithelium was observed but a significant difference in the labelling index of the olfactory epithelium was observed after 20 days of exposure to 600 or 1000ppm. The NOAEC for nasal effects was 200ppm (704mg/m^3).

"In conclusion, the NOAEC for local and systemic toxicities induced by vinyl acetate inhalation are similar across most of the studies reported. Where the values differ, close inspection of the experimental protocol or interpretation of results reveals the basis of the difference. The 2 year combined chronic toxicity and carcinogenicity study on Sprague-Dawley rats and CD-1 mice (Hazleton 1988b, Bogdanffy *et al*., 1994b) was considered to be the most appropriate study from which to derive the NOAEC values.

"Local toxicity (respiratory tract effects). The **$NOAEC_{local}$** is 50ppm (176mg/m^3).

"Systemic toxicity (bodyweight effects). The **$NOAEC_{sys}$** is 50ppm (equivalent to 176mg/m^3)." (References cited in ECHA REACH, 2019a).

The New Zealand EPA classifies vinyl acetate as a 6.9B substance – a substance that is harmful to human target organs or systems (EPA, 2019).

The ECHA REACH Dossier for vinyl acetate summarised the reproductive/ developmental toxicity in experimental animals:

Reproductive toxicity

"There are sufficient data available for assessment from a 2-Generation study in rats. Some minor and slight effects on male fertility, not forming a specific pattern, were observed in the high dose group receiving 5000ppm orally in drinking water, which also induced slight parental toxicity. No effects were observed on any parameters of female fertility. Based on the available data it can be concluded that Vinyl Acetate shows no specifically toxic effects on fertility. A conservative **NOAEL** of 1000ppm in drinking water could be derived for male fertility, and 5000ppm for female fertility.

"Another study on testicular genotoxic effects of VA after administration of very high doses using a non-physiological route of exposure **(i.p.**) was considered of no regulatory relevance.

"All in all, a clear and conservative NOAEL of 1000ppm in drinking water (76 to 145mg/kg/day [differences are due to the decline in water consumption relative to body weight that occurred over this time period]) could be derived for male fertility. No indication of effects in females in doses up to 5000ppm in drinking water (431 to 765mg/kg/day [differences are due to the decline in water consumption relative to body weight that occurred over this time period]) were detected.

"These data are sufficient for an adequate hazard and risk assessment. Based on the available data, no classification for fertility (RF) is justified."

Endocrine disruptive potential

"A non-conventional two-generation reproduction toxicity study in which Sprague Dawley CD rats were treated orally with vinyl acetate over two generations (Mebus *et al*., 1995) yielded the following findings that were interpreted as being substance-related (and not, for example, secondary to the reduced water consumption):

- Although not statistically significant, the **F1** fertility index of the 5000-ppm group was lower than that for the control group. The number of litters produced in the high-dose F1 generation was slightly reduced, and this was interpreted by the authors as being caused by reduced fertility.
- When the high-dose group F1 males were cross-mated with the corresponding control F1 females, fewer pups were produced. This was caused by poor mating performance."

"In the F1 cross-mating, there were 12 control males available to mate 24 females from the 5000-ppm group and 13 males from the 5000-ppm group available to mate 25 control females. The pregnant females were killed on gestation day 13 and the intrauterine contents examined. The mating index of the female controls/5000-ppm males was 19/25 females mated while the mating index for the 5000-ppm females/control males was 23/24 female mated. The fertility index of the female control/5000-ppm male mating was 19/19 pregnancies while the fertility index for the 5000-ppm female/control male mating was 22/23 pregnancies. Mebus *et al*. suggested a possible male-specific effect based on the reduced fertility in the F1a 'standard' mating and the reduced mating index in the F1b cross-mating. However, the data do not support this suggestion. First, all of the 13 males in the 5000-ppm group used in the cross-mating experiment produced a pregnancy. This suggests that the reduced fertility index in the F1a mating was probably due to the female animals, not the males used for breeding. The reduced mating index in the F1b female control/male 5000ppm animals (despite all of the males producing at least one pregnancy) is not easily explained although the method used to mate these animals was extremely unconventional.

"Therefore, although the Mebus *et al*. (1995) indicated that the non-statistically significant finding might be attributed to male fertility, the data do not support this suggestion. The variances observed in this study, and the non-standard, non-guideline approach do not lend enough credible evidence to support that the findings are linked to an endocrine mode of action, nor do they support that there would be sufficient evidence to conclude that endocrine disruption had occurred."

Developmental toxicity

"There are sufficient data to assess the potential of vinyl acetate to cause developmental toxicity. Data is available from:

- an oral drinking water developmental toxicity study in rats
- an inhalation study also in rats
- a drinking water two-generation study in rats
- a **DRF** and a main developmental toxicity study in rabbits.

"In a developmental toxicity study in rats, administration of vinyl acetate in the drinking water during the period of organogenesis (days 6 to 15 of gestation, inclusive) at dose levels up to and including those which produced a degree of drinking water unpalatability did not elicit any developmental effects. Thus, a developmental NOAEL of 5000ppm **v/v** in drinking water (477mg/kg/day) could be determined.

> "In another developmental toxicity study in rats after administration of VA by the inhalation route at concentrations up to and including those which produced maternal toxicity did not elicit embryolethality or teratogenicity. At the highest concentration employed (1000ppm v/v vinyl acetate), there was evidence of growth retardation of the foetuses, however this was considered to be a secondary effect of marked maternal growth retardation, and not a direct effect of exposure to vinyl acetate. Thus, the developmental NOAEL of 1000ppm v/v could be determined for inhalation exposure. Unfortunately, no data were available on the degree of absorption of VA.
>
> "In a two-generation study in rats, a minor, slight and inconsistent decrease in pup weight on day 21**pp** in the F1 generation, but not in the **F2**, was the only finding of a developmental effect in the high dose group receiving 5000ppm orally in drinking water. This is considered secondary to a decreased body weight gain and water consumption of dams during lactation. Consequently, 5000ppm in drinking water (431 to 765mg/kg/day [differences are due to the decline in water consumption relative to body weight that occurred over this time period) was found to be the NOAEL for developmental toxicity. Moreover, it can be concluded that VA shows no specifically toxic effects on development.
>
> "In a developmental toxicity study in rabbits, no developmental or maternal toxicity was observed, though the study, based on a DRF, was clearly planned in order to aiming at some maternal toxicity, thus fulfilling the criteria of a valid OECD 414 Guideline study. A NOAEL of 100mg/kg/day could be determined, which is also supported by the fact that no developmental toxicity (litter size, pup weight, external anomalies) was observed in the DRF study at 200mg/kg/day, a dose that caused significant maternal toxicity.
>
> "Furthermore, in none of these studies, any indications for a developmentally toxic potential of vinyl acetate could be observed." (References cited in ECHA REACH, 2019b).

The New Zealand EPA classifies vinyl acetate as a 6.8B substance – a substance that is a suspected human reproductive or developmental toxicant (EPA, 2019).

The ECHA RAR review of vinyl acetate summarised the genotoxic potential in experimental animals and *in vitro* test systems:

> "Vinyl acetate is negative in bacterial mutagenicity tests.
>
> "In mammalian cell cultures various cytogenetic effects were induced in the absence of S-9 mix (chromosomal aberrations, micronuclei, **SCE**) and in the presence of S-9 mix (SCE; chromosomal aberrations and micronuclei not analysed with S-9 mix). The lowest positive concentrations ranged from 0.1 to 0.2mmol/l. A positive mouse lymphoma assay is in line with these results, but it cannot be deduced whether the positive effect is due to chromosomal or to gene mutations (no colony sizing). Mammalian cell culture investigations on **DNA** strand breaks (**DSB**) and DNA protein crosslinks (**DPX**) were negative (DSB), or extremely high concentrations were needed for positive effects (DPX).
>
> "Very few reliable data are available on the *in vivo* mutagenicity of vinyl acetate. A weak induction of micronuclei in mouse bone marrow cells was clearly limited to intraperitoneal doses in the LD50 range (1000 and 2000**mg/kg bw**). In rats no induction of micronuclei was observed in spermatids (screening assay with intraperitoneal doses up to 1000mg/kg bw). Further tests on induction of micronuclei or chromosomal aberrations were of too low reliability.

> "Also in an **SCE** test with rats positive effects were weak and limited to high and probably highly toxic intraperitoneal doses (370 and 470mg/kg bw). Such weak increases in SCE frequencies may well be induced by unspecific effects on the cell cycle.
>
> "No specific DNA binding was observed in rat livers after inhalation or oral administration.
>
> "Induction of sperm abnormalities in mice again was limited to doses in the toxic range. Furthermore, it is not specific for mutagens.
>
> "No clear conclusion can be drawn from a human study on the possible induction of chromosomal aberrations in workers exposed to vinyl acetate.
>
> "Genotoxicity data on vinyl acetate metabolites are in line with the hypothesis that vinyl acetate genotoxicity is mediated by acetaldehyde. The genotoxicity of acetaldehyde is possibly limited to an overloading of defence mechanisms.
>
> "Altogether, vinyl acetate has a mutagenic potential, which is preferentially expressed as clastogenesis. The data on *in vivo* genotoxicity are difficult to interpret, since their majority is of low reliability, or the effects are not specific to mutagenicity. The most important effect, a weak induction of micronuclei in mouse bone marrow, is limited to intraperitoneal doses of high toxicity. Therefore, it is unlikely that the genotoxic potential of vinyl acetate is expressed in germ cells in man. However, genotoxic effects locally in directly exposed tissues (site of first contact) cannot be excluded; the occurrence and strength of the effects will be dependent on the metabolic capacity of the directly exposed tissue." (References cited in ECHA RAR, 2008).

The New Zealand EPA classifies vinyl acetate as a 6.6A substance – a substance that is a known or presumed mutagen (EPA, 2019).

4.2 Cancer

The International Agency for Research on Cancer [**IARC**] evaluation of vinyl acetate concluded that:

> There is *inadequate evidence* in humans for the carcinogenicity of vinyl acetate.
>
> There is *limited evidence* in experimental animals for the carcinogenicity of vinyl acetate.

With an overall evaluation that:

> Vinyl acetate is *possibly carcinogenic to humans (Group 2B)*.

In making the overall evaluation, the Working Group took into account the following evidence:

> i. Vinyl acetate is rapidly transformed into acetaldehyde in human blood and animal tissues.
>
> ii. There is *sufficient evidence* in experimental animals for the carcinogenicity of acetaldehyde (IARC, 1987b). Both vinyl acetate and acetaldehyde induce nasal cancer in rats after administration by inhalation.
>
> iii. Vinyl acetate and acetaldehyde are genotoxic in human cells *in vitro* and in animals *in vivo*. (IARC, 1995).

The US National Toxicology Program [**NTP**] Report on Carcinogens [**RoC**], Fourteenth Edition has no evaluation on the carcinogenic potential of vinyl acetate (NTP RoC, 2019).

The New Zealand EPA classifies vinyl acetate as 6.7B – A substance that is a suspected human carcinogen (EPA, 2019).

Humans

The ECHA RAR review of vinyl acetate summarised the carcinogenic potential in exposed workers:

> "In a cohort study, 4806 male workers who were exposed to 19 different chemicals (vinyl chloride, polyvinylchloride dust, chlorinated solvents, acrylates, acrylonitrile and others) including vinyl acetate, between the years 1942 and 1973 had an excess risk of cancer of the respiratory system and the **CNS**. A subgroup (of cases with lung cancer) with undifferentiated large cell lung cancer was associated to a slightly higher cumulative exposure to vinyl acetate (Waxweiler *et al*., 1981).
>
> "A nested case-control study (Ott *et al*., 1989) was undertaken in a cohort of 29139 men employed in two chemical manufacturing facilities and a research and development center, who had died in 1940–1978 with non-Hodgkin`s lymphoma, multiple myeloma, lymphocytic or nonlymphocytic leukemia. Exposure **odds ratios** (**OR**) were examined in relation to 111 work areas, 21 specific chemicals (OR based on an ever/never basis), and 52 chemical activity groups. Exposure to vinyl acetate was associated with non-Hodgkin's lymphoma in seven of 52 men (OR 1.2), multiple myeloma in three of 20 men (OR 1.6), non-lymphocytic leukemia in two of 39 men (OR 0.5), and with lymphocytic leukemia in two of 18 men (OR 1.8). Examination of OR related to the exposure duration was not done because of the OR <1.3 or number of cases <4." (Reference cited in ECHA RAR, 2008).

Animals

The ECHA RAR review of vinyl acetate summarised the carcinogenicity data in experimental animals:

> "Vinyl acetate induced an increased number of nasal tumors (mainly papillomas and squamous cell carcinomas) in various regions of the nasal mucosa of rats after long-term inhalation. The total incidence was significantly increased at a concentration of 600ppm, but a single papilloma already developed at 200ppm. No significant tumor response was seen in mice after long-term inhalation of vinyl acetate vapour. Occasionally single squamous cell tumors occurred at other sites of the respiratory tract in rats and mice.
>
> "Although the complete report was not available, published information from a recent oral cancer study in F344 rats and BDF1 mice (Umeda *et al*. 2004a) demonstrated significantly increased rates of squamous cell tumors in the oral cavity (rats and mice), esophagus and forestomach (mice) after a 2-year administration of 10000ppm vinyl acetate with the drinking water (equivalent mean doses in rats were 442**mg/kg bw/d** for males, 575mg/kg bw/d for females, in mice 989mg/kg bw/d for males, 1418mg/kg bw/d for females). Maximum increase of tumor incidences was found in the oral cavity in both species. Squamous cell carcinomas were already observed at a dose of 400ppm in female rats (31mg/kg bw/d). Consistently in another life-time study on a breeding and offspring generation of mice (Maltoni *et al*., 1997) which did not met actual standards on cancer bioassays, squamous cell

tumors were also observed with increased incidences in several sites of the gastrointestinal tract (oral cavity, tongue, esophagus, forestomach) at a concentration of 5000ppm in the drinking water (calculated dose 780mg/kg bw/d). In addition, higher incidences of adenocarcinomas of the glandular region of the stomach were found in high-dose male breeders. Also some other organs (lung, liver, uterus) showed increased rates of benign and malignant tumors compared to that of the control groups. Tumors of the liver and the uterus have also been seen in the Lijinsky study (Lijinsky and Reuber, 1983). However, both studies hampered from methodical insufficiencies. Further, these data were inconsistent to the absence of parenchymal tumors in other more valid studies. Therefore interpretation of these tumors remains unclear. With respect to the carcinogenic potential of vinyl acetate, the results of Lijinsky and Reuber (1983) were considered not to be reliable due to several methodological deficiencies. No indication for an increased incidence of enzyme-altered liver foci was seen in another study (Laib and Bolt, 1986).

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

"Recently published data on rats exposed to drinking water containing 1000 or 5000ppm vinyl acetate confirmed significant increases in squamous cell carcinomas of the oral cavity and the forestomach (Minardi *et al*., 2002). Treatment of offsprings resulted in higher tumor rates than in rats with treatment begin at week 17 of life. However, this study has a number of limitations in its design. Thus, tumor response along the gastrointestinal could be interpreted to be supportive to the results from the Umeda study." (References cited in ECHA RAR, 2008).

Soffritti *et al*. (2008) reported a series of non-guideline experiments using Sprague–Dawley rats, Wistar rats and Swiss mice. The mouse study was originally reported by Maltoni *et al*. (1997 cited in ECHA RAR, 2008), and the study with Sprague–Dawley rats by Minardi *et al*. (2002 cited in ECHA RAR, 2008).

"A similar protocol was applied for all three experiments. Vinyl acetate monomer was administered by ingestion in drinking water supplied *ad libitum* at the concentrations of 5000, 1000 or 0ppm to 17-week-old males and females (breeders) and 12-day-old embryos (offspring). The treatment lasted 104 weeks in rats and 78 weeks in mice. All animals were monitored until natural death (130–150 weeks).

"In the tested conditions, vinyl acetate monomer was demonstrated to be a multipotent carcinogenic agent, inducing malignant tumours of the oral cavity, tongue, oesophagus and forestomach in both strains of rats and mice. A slight increase in the incidence of adenomas/carcinomas of the lung and of malignant tumours of the uterus in mice was also observed. Furthermore, the carcinogenic effects were strongly increased when exposure began during foetal life" (Soffritti *et al*., 2008).

4.3 Absorption, distribution, metabolism and excretion

The ACGIH® review of vinyl acetate summarised the **ADME**:

> "In the presence of rat or mouse liver homogenates or human plasma and whole blood, VA is rapidly converted to acetic acid and **AA** by an enzyme-mediated hydrolysis (Simon *et al*., 1985; European Commission, 2008). These metabolites lead to cytotoxicity, cell death and cell proliferation (Bogdanffy and Valentine, 2003). The biological effects of VA *in vivo* probably result from its carboxylesterase-dependent metabolism to acetic acid and AA (via vinyl alcohol). AA is converted to acetic acid catalysed by aldehyde dehydrogenase and nicotinamide adenine dinucleotide (**NAD**). These metabolic steps release protons, which with the acetic acid reduce the cellular pH that may have non-specific cytotoxic and proliferative effects (Albertini, 2013). AA is the major specific mutagen (Albertini, 2013), and it is known to be clastogenic (Plowchalk *et al*., 1997).
>
> "Rats exposed to VA by inhalation increased circulating and expired air AA concentrations post-exposure (Filov, 1959). VA exposure resulted in decreased pH in respiratory epithelial cells (Lantz *et al*., 2003; Nakamoto *et al*., 2005).
>
> "Radio-labeled VA was administered nose-only to 4 CD rats. Immediately after administration, there was wide tissue distribution with concentration in the ilium, harderian and salivary glands. During a 96-hour collection period, the mean proportions of the recovered radioactivity were 74.6% in expired air, 4.8% in urine and 3.6% in feces. The major portion of radioactivity was eliminated in the first 24 hours following exposure. The major metabolite was carbon dioxide (European Commission, 2008).
>
> "In rats, the proportion of VA removed from the airstream was highest at the lowest exposure concentrations. More than 94% was taken up in the nasal cavity below 76ppm. With increasing exposure (76 to 550ppm), extraction decreased progressively to about 40% and plateaued at approximately 2000ppm (European Commission, 2008).
>
> "In rats, metabolic pathways became saturated when VA exposure exceeded 2320mg/m^3 (650ppm) (European Commission, 2008).
>
> "Blood flow extraction accounts for less than 15% of VA deposition. VA has a blood half-life between less than 1 minute and 4.1 minutes (European Commission, 2008).
>
> "Metabolism occurs faster in olfactory than in respiratory mucosa, which may partially explain the nasal lesions induced by VA in rodents (IARC, 1995).
>
> "AA was detected in homogenates prepared from rodent oral cavity scrapings after inhalation of VA (Morris *et al*., 2002). AA is produced endogenously, and there is *in vivo* evidence that aldehyde dehydrogenase in humans limits AA presence and hence probably limits the mutagenicity of VA (Albetini, 2013).
>
> "Hybrid computational fluid dynamics/physiologically based pharmacokinetic (**PBPK**) modelling predicted equivalent VA nasal tissue doses in humans and rats at equivalent exposure concentrations (Andersen *et al*., 2002). PBPK modelling by other investigators drew the same conclusion and suggested that the intracellular pH would drop significantly in the olfactory cells at exposures above 50ppm (Bogdanffy *et al*., 1999). The model was later validated in humans for the 1–10ppm range (Hinderliter *et al*., 2005)." (Reference cited in ACGIH®, 2018,).

The ACGIH® review of vinyl acetate noted:

> "In a controlled human experiment, 5 volunteers inhaled radio-labeled VA during resting and light exercise at 1, 5 and 10ppm. VA and AA were sampled from a probe in the nasopharyngeal cavity and analysed by ion trap mass spectrometry. Measurements were taken every 0.8 seconds in an exposure period of 2 to 5 minutes. An acoustic rhinometry system was used to measure the cross-sectional area and volume of the nasal cavity. Mean nasopharyngeal concentrations of VA and AA appeared to increase in a linear fashion with increasing exposure over this range (Hinderliter *et al*., 2005)." (ACGIH®, 2018).

The ECHA RAR review of vinyl acetate summarised the mechanistic data for toxicity and carcinogenicity:

> "In conclusion, vinyl acetate exposure produced tumors at the site of first contact along the exposure routes. A thresholded mode of carcinogenic action is thought to be active. The observed tumor responses are reflecting the target site-specific enzyme activities:
>
> "Following inhalation and oral exposure vinyl acetate is rapidly hydrolysed by carboxylesterases leading to the formation of acetic acid and acetaldehyde which is further converted into acetic acid in the presence of aldehyde dehydrogenases. Intracellular aldehyde dehydrogenase activity is limited, at higher concentrations of vinyl acetate it will not be sufficient for the oxidation of generated acetaldehyde. Thus, at high vinyl acetate concentrations non-physiologically high concentrations of acetaldehyde are produced. Acetaldehyde is a physiological intermediate with low background concentrations. Its adverse effects (genotoxicity and mutagenicity) are limited to non-physiologically high concentrations. Therefore, a threshold mode of action is assumed for vinyl acetate.
>
> "Above threshold concentrations, cytotoxicity (only at the olfactory mucosa), mitogenic actions and genotoxic actions occurred.
>
> "Cytotoxicity mainly contributed by acetic acid is the earliest lesion in the olfactory mucosa. Next stages in the continuum to tumor development include the responsive restorative cell proliferation and simultaneously occurring genotoxic effects of acetaldehyde.
>
> "Increased cell proliferative activity was observed at high concentrations of acetaldehyde or vinyl acetate. Its occurrence was not linked to cell toxicity as a precondition.
>
> "Data on vinyl acetate are in line with the idea that vinyl acetate genotoxicity is mediated by acetaldehyde. Increasing concentrations of acetaldehyde produce genotoxic actions at the site of contact. It has to be taken into consideration that acetaldehyde occurs naturally in mammalians cells and is part of the physiological cellular metabolism.
>
> "The systemic bioavailability of vinyl acetate or its metabolite is low (cf. 4.1.2.1). In vivo genotoxicity tests showed that systemic genotoxicity appears to be limited to toxic doses. This is in line with the absence of systemic carcinogenic effects.

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

"Overall, it is considered that the critical events in vinyl acetate carcinogenesis do fit to the criteria for the exceptional cases where genotoxic action is thought to be thresholded." (ECHA RAR, 2008).

5.0 Exposure standards

IN THIS SECTION:

5.1 Other exposure standards

Table 3 below shows vinyl acetate exposure standards from around the world, as published by the Institute for Occupational Safety and Health of the German Social Accident Insurance (**IFA**, 2019).

JURISDICTION OR ADVISORY BODY	8-HOUR LIMIT VALUE		SHORT-TERM LIMIT VALUE	
	ppm	mg/m³	ppm	mg/m³
Australia	10	35	20	70
Austria	5	17.6	10	35.2
Belgium	5	17.6	10[1]	35.2[1]
Canada – Ontario	10		15	
Canada – Québec	10	35	15	53
Denmark	10	30	20	60
European Union	5[2]	17.6[2]	10[1,2]	35.2[1,2]
Finland	5	18	10[1]	35[1]
France	5[3]	17.6[3]	10[3]	35.2[3]
Germany – AGS	5	18	10[1]	36[1]
Ireland	5	18	10[4]	35[4]
Italy	5	17.6	10	35.2
Latvia	5	17.6	10[1]	35.2[1]
New Zealand	10	35	20	70
People's Republic of China		10		15[1]
Poland		10		30
Romania	5	17.6	10[1]	35.2[1]
Singapore	10	35	15	53
South Korea	10		15	
Spain	10	36	15	54
Sweden	5	18	10[1]	35[1]
Switzerland	10	35	10	35
The Netherlands		18		36
Turkey	5	17.6	10[1]	35.2[1]
USA – **NIOSH**			4[5]	15[5]
UK[6]	10	36	20	72

TABLE 3: Exposure standards for vinyl acetate from around the world

It is noted that the only organisations from whom we obtained information as to how and why they set occupational exposures standards on vinyl acetate were ACGIH®, SCOEL and **DFG**.

[1] 15 minutes average value.

[2] Indicative Occupational Exposure Limit Value (**IOELV**).

[3] Restrictive statutory limit values.

[4] 15 minutes reference period.

[5] **Ceiling limit value**.

[6] The UK Advisory Committee on Toxic Substances has expressed concerns that health may not be adequately protected because of doubts that the limit was not soundly-based. These **OEL**s were included in the published UK 2002 list and its 2003 supplement, but are omitted from the published 2005 list.

5.2 ACGIH®

The American Conference of Governmental Industrial Hygienists [ACGIH®] review recommended a **TLV-TWA** of 10ppm [35mg/m^3] for occupational exposure to vinyl acetate to minimise the potential risk of respiratory tract irritation reported in animals exposed to vinyl acetate vapour above 50ppm, the NOAEL for microscopic evidence of respiratory tract irritation in SD rats and CD-1 mice (Bogdanffy *et al*., 1994a cited in ACGIH®, 2018).

The ACGIH® also recommended a **TLV-STEL** of 15ppm [53mg/m^3] for vinyl acetate to minimise the potential for eye and upper respiratory tract irritation reported in short-term exposure to humans at 22ppm and 72ppm (ACGIH®, 2018).

The ACGIH® assigned a carcinogenicity notation of A3, Confirmed Animal Carcinogen with Unknown Relevance to Humans, based on the multiple site tumorigenic responses in male rats exposed by inhalation to vinyl acetate above 600ppm (Bogdanffy *et al*., 1994a cited in ACGIH®, 2018). F344 rats exposed to vinyl acetate in the drinking water at 2,500mg/L displayed excess risks of cancer (Lijinsky and Reuber, 1983 cited in ACGIH®, 2018). The ACGIH® noted that there was evidence of genotoxicity in human and animal cells *in vitro*, and in animal cells *in vivo* (ACGIH®, 2018).

The ACGIH® also noted that there was no reliable epidemiological evidence to assess potential health impacts in exposed workers; there was insufficient evidence to recommend **Skin** or **RSEN** notations; and, the limited evidence from human patch tests and LLNA results did not support a **DSEN** notation (ACGIH®, 2018).

5.3 SCOEL

The Scientific Committee on Occupational Exposure Limits [SCOEL] assessment of vinyl acetate recommended a STEL of 10ppm and an 8-hour TWA at half this value, 5ppm, for occupational exposures to vinyl acetate (SCOEL, 2005).

The rationale for their conclusions included:

> "Vinyl acetate was found to have genotoxic effects *in vitro*, for example, 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 50ppm (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 50ppm (175mg/m^3). This confirms early industrial information on concentrations up to 10ppm being unlikely to produce respiratory or ocular irritation in most workers, whereas concentrations above 20ppm 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: 10ppm, STEL: 20ppm) 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 50ppm. A threshold for sensory irritation may be expected to be lower. There are limited observations in humans (ACGIH 1992) of a NOAEL for irritancy at 10ppm. Considering these experimental and human data on irritancy and the experimentally observed local carcinogenicity at higher concentrations, a STEL is set at 10ppm, and an OEL (8h-TWA) at half of this value."
>
> "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." (SCOEL, 2005).

SCHER (2008) concurred with the SCOEL proposed OEL of 5ppm (17.6mg.m^3) (SCHER 2008).

> "On the background of cancer risks and repeated dose toxicity, air concentrations of VA at the workplace should be controlled to a level in the range of 17.6mg/m^3 (critical exposure level). The SCHER agrees to this proposal and refers to the SCOEL, which has proposed an EL of 5ppm (17.6mg/m^3). SCHER also supports conclusion iii) for repeated dose toxicity after inhalation for scenario 2 (manufacturing of formulations and products) to reduce air concentration to the OEL of 5ppm." (SCHER 2008).

5.4 DFG

The Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) review of vinyl acetate recommended no **MAK** value; no Peak limitation, Skin or Sensitisation notations; **Carcinogenicity Category, 3A**; and, no Pregnancy Risk or Germ cell mutation classifications (DFG, 2005, 2018,).

The rationale for their conclusions included:

"In two epidemiological studies with exposure to a mixture of substances, no statistically decisive 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, however, and the influence of smoking habits was not excluded. The data are therefore not meaningful.

"In 2-year drinking water studies with F344 rats and BDF1 mice, tumours of the oesophagus and oral cavity (rats, mice) and stomach and larynx (mice) were induced at the highest concentration of 10000mg/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**ml/m³**, 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 750ml/m³ 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 600ml/m³. On the other hand, the irritative effects of vinyl acetate are greater than those of acetaldehyde.

"The findings in studies of the carcinogenicity of vinyl acetate are explained by the local cytotoxicity resulting from the local metabolism to acetaldehyde and acetic acid on the one hand, and by the genotoxic effects of its metabolite acetaldehyde on the other hand. The hypothesis that the epigenetic effects are more important than the genotoxic effects at present does not seem adequately demonstrated. There is much to indicate, however, 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. This is clear from the non-linear course of the dose-effect relationships in the carcinogenicity studies. There are, however, no studies available which validly predict the amounts of acetaldehyde and acetic acid formed at the site of action for vinyl acetate to be classified in Carcinogenicity category 5. In addition, the local irritation threshold in man must be better investigated. Until the necessary data become available, the substance has been provisionally classified in Carcinogenicity category 3A and the previous MAK value has been withdrawn.

"The systemic NOAEL (reduced body weights in mice) from the inhalation carcinogenicity study is 50ml/m³ (175mg/m³). With 100 % retention this would be a daily dose of about 285mg/kg body weight. Calculated for a person of 70 kg, this means about 12250mg. The models of Fiserova-Bergerova *et al*. (1990) and Guy and Potts (1993) predict absorption of 541 and 68mg, respectively, after exposure to a saturated aqueous solution of 2000cm² for one hour. Thus, in the least favourable case, dermal exposure should lead only to absorption of less than one tenth of the critical amount. The volatility of the substance and the irritative effects are very high and dermal exposure to the undiluted substance for longer periods is therefore unlikely. Designation with an "**H**" is therefore not necessary.

"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. There are no data available for the sensitizing effects on the respiratory tract; it is, therefore, not possible to give a definitive evaluation of the sensitizing effects of vinyl acetate. The substance is therefore not designated with an "**S**".

> "Vinyl acetate was found to have genotoxic effects *in vitro*, for example, 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 classified as a germ cell mutagen." (References cited in DFG, 2005).

6.0 Analytical methods for the assessment of airborne vinyl acetate

One method available in New Zealand to measure vinyl acetate exposure is using Compendium Method TO-15 (US EPSA, 1999).

Using this method, an air sample is collected into an evacuated stainless steel canister. A known volume of the sample is drawn through a solid multisorbent concentrator, and following thermal desorption, is analysed by **GC-MS/MS**.

This method can reliably measure vinyl acetate concentrations below 0.5ppm.

7.0
Discussion

WorkSafe's WES for vinyl acetate has been unchanged since adoption in 1994.

The toxicological database reviewed above indicates vinyl acetate is locally toxic to humans, causing eye and upper respiratory tract irritation; and locally and systemically toxic to laboratory species, causing eye and respiratory tract irritation, body weight loss, and nasal and gastrointestinal tumours in rats.

Based on the aforementioned documentation, informed by the conclusions of the ACGIH®, SCOEL and DFG reviews, and in particular the findings listed below, WorkSafe considers its current WES-TWA of 10ppm [35mg/m^3] and a WES-STEL of 20ppm [70mg/m^3] to be inadequate to protect workers exposed in the workplace, based on current knowledge:

- Vinyl acetate has the potential to induce eye and respiratory tract irritation in exposed workers and experimental animals (ECHA RAR, 2008; SCOEL, 2005).
- Vinyl acetate has the potential to induce nasal tumours in rats and mice after inhalation exposures and tumours in the gastrointestinal tract after oral administration, with concurrent non-neoplastic lesions (ECHA REACH, 2019; ECHA RAR, 2008; SCOEL, 2005).
- The mutagenic potential of vinyl acetate appears as clastogenesis at relatively high doses/ concentrations, due to, it is postulated, when levels of the genotoxic metabolite acetaldehyde overload cellular defence mechanisms (ECHA RAR, 2008; IARC, 1995).
- The mechanism(s) by which vinyl acetate induces cancer in rodent nasal cavities has not been fully elucidated, but it has been suggested involves intracellular acidification and cytotoxicity by the metabolite acetic acid, then restorative cell proliferation in the presence of DNA-reactive and genotoxic metabolite acetaldehyde (ECHA RAR, 2008; SCOEL, 2005).
- The ACGIH® proposed a TLV-TWA for vinyl acetate at 10ppm [35mg/m^3], based on a NOAEL of 50ppm for respiratory tract irritation in SD rats and CD-1 mice, with a TLV-STEL at 15ppm [53mg/m^3], based on irritation reports from short-term exposure to individuals at 22ppm (ACGIH®, 2019).
- The SCOEL recommended a STEL of 10ppm, based on the 50ppm NOAEL from rodents and a NOAEL of 10ppm reported for irritancy in exposed humans, and an 8-hour TWA proposed at 5ppm. The SCOEL noted that a threshold for sensory irritation is likely to be lower than that for cellular irritation (SCOEL, 2005).
- The SCHER concurred with SCOEL that 5ppm [17.6mg/m^3] was the critical exposure level and the proposed OEL of 5ppm (SCHER, 2008).
- The DFG withdrew their MAK Value of 10ppm [35mg/m^3] for vinyl acetate due to lack of robust data to establish a threshold (DFG, 2005).
- The proposed WES-TWA of 5ppm [20mg/m^3] for vinyl acetate is set to be protective against all non-carcinogenic endpoints and below concentrations where metabolites acetic acid and acetaldehyde become toxicologically significant in phenotypically normal individuals.

- The proposed WES-STEL of 10ppm [35mg/m^3] for vinyl acetate is set to be protective against peak concentrations triggering acute respiratory tract irritation. A WES-STEL is justified for vinyl acetate as acute respiratory tract irritation is the critical endpoint, and peak as well as cumulative exposures should be limited to adequately protect exposed workers.
- A *skin* notation is not justified for vinyl acetate, based on the volatility of vinyl acetate limiting dermal exposure contribution, and reported low toxicity after dermal administration (SCOEL, 2005; DFG, 2005; ECHA RAR, 2008).
- Available information indicates that while vinyl acetate may be a dermal sensitiser in experimental animals, there is insufficient evidence about dermal and respiratory sensitisation in exposed humans, so a ***dsen*** or ***rsen*** notation is not warranted (ACGIH®, 2018; SCOEL, 2005).
- WorkSafe notes the lack of any robust epidemiological data to facilitate setting a WES.

8.0
Recommendations

WorkSafe considers its current WES-TWA of 10ppm [35mg/m^3] and a WES-STEL of 20ppm [70mg/m^3] of vinyl acetate to be inadequate to protect workers exposed in the workplace, based on current knowledge.

It is proposed that WorkSafe:

1. adopt a WES-TWA for vinyl acetate of 5ppm [18mg/m^3]
2. adopt a WES-STEL for vinyl acetate of 10ppm [35mg/m^3].

Noting that the recommended WES-TWA of 5ppm and WES-STEL of 10ppm for vinyl acetate may not eliminate all risk, due to the uncertainties the impact of genotoxicity in the carcinogenic mechanism and the lack of a threshold for sensory irritation, exposures should be minimised.

Appendices

IN THIS SECTION:

Appendix 1: Glossary

TERM	MEANING
AA	Acetaldehyde.
ACGIH®	The American Conference of Governmental Industrial Hygienists (ACGIH®) is a member-based organisation, established in 1938, that advances occupational and environmental health. Examples of this include their annual edition of the TLVs® and BEIs® book and work practice guides. Store at: www.acgih.org/store
ADME	Absorption, Distribution, Metabolism and Excretion.
AGS	Ausschuss für Gefahrstoffe [Committee for Hazardous Substances] is a consultative body of the German Federal Ministry of Labour and Social Affairs on issues of the Ordinance on Hazardous Substances. Administered by the BAuA.
ATSDR	Agency for Toxic Substances and Disease Registry is a federal public health agency of the US Department of Health and Human Services.
BrdU	2-Bromo-5”deoxyuridine.
Carcinogen Category, 3A	DFG MAK designation: Substances that cause cancer in humans or animals or that are considered to be carcinogenic for humans for which the criteria for classification in Category 4 or 5 are in principle fulfilled. However, the database for these substances is insufficient for the establishment of a MAK or BAT value.
Ceiling or Ceiling Limit Value	Ceiling Limit Value – absolute exposure limit that should not be exceeded at any time.
CNS	Central nervous system.
DGUV-IFA	Deutschen Gesetzlichen Unfallversicherung ([German Social Accident Insurance] – Institut für Arbeitsschutz [Institute for Occupational Safety and Health].
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation), the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Federal Republic of Germany. The science-based MAK values are recommended to the German Minister of Labour and Social Affairs for possible adoption under the German Hazardous Substances Ordinance.
DPX	DNA-protein cross-links.
DRF	Dose range finding.
DSB	DNA strand break.
dsen	A substance that can ‘sensitise’ the skin, inducing a state of hypersensitivity to it, so that on subsequent exposures, an allergic reaction can occur (which would not develop in non-sensitised individuals). It is uncommon to become sensitised to a compound after just a single reaction to it. A WorkSafe term.
DSEN	A notation indicating the substance is a dermal sensitiser. DSEN is used in place of SEN when specific evidence of sensitisation by the dermal route is confirmed by human or animal data. An ACGIH® term.
ECHA	The European Chemicals Agency (an agency of the European Union).
EPA	The New Zealand Environmental Protection Authority.
EU	European Union.
F1	First filial generation.
F2	Second filial generation.
FID	Flame ionisation detection.
GC-MS/MS	During analysis by gas chromatography-tandem mass spectrometry (GC-MS/MS) analytes are separated in the gas chromatograph. They elute from the analytical column into the MS/MS which consists of two scanning mass analysers separated by a collision cell. Fragments selected in the first analyser react with an inert gas in the collision cell resulting in further fragmentation. These daughter product ions are then analysed by the third quadrupole.

TERM	MEANING
GLP	Good Laboratory Practice.
"H"	DFG MAK designation: *danger of percutaneous absorption*. Equivalent to the 'skin' notation in the WorkSafe WES special guide.
HSNO	Hazardous Substances and New Organisms Act 1996, New Zealand.
IARC	International Agency for Research on Cancer, an agency of the World Health Organization.
IFA	Institut für Arbeitsschutz der Deutschen Gestzlichen Unfallversicherung [Institute for Occupational Safety and Health of the German Social Accident Insurance].
IOELV	Indicative Occupational Exposure Limit Value (health-based, SCOEL parameter).
i.p.	Intraperitoneal.
LC_{50}	Lethal Concentration for 50% of the test population.
LD_{50}	Lethal Dose for 50% of the test population.
LLNA	Local lymph node assay.
LOAEL	Lowest Observed Adverse Effect Level.
MAK	Maximale Arbeitsplatz-Konzentration, (maximum workplace concentration) is defined as the maximum concentration of a chemical substance (as gas, vapour or particulate matter) in the workplace air which generally does not have known adverse effects on the health of the employee nor cause unreasonable annoyance (for example, by a nauseous odour) even when the person is repeatedly exposed during long periods, usually for 8 hours daily but assuming on average a 40-hour working week. A value set by the DFG.
mg	Milligram or one thousandth of a gram.
mg/kg	Milligrams per kilogram.
mg/kg b.w./ mg/kg bw	Milligram of substance per kilogram body weight.
mg/kg b.w./ day/ mg/kg bw/d	Milligram of substance per kilogram body weight per day.
mg/L	Milligram of substance per litre.
mg/m^3	Milligrams of substance per cubic metre of air.
ml/m^3	Millilitres of substance per cubic metre of air.
NAD	Nicotinamide Adenine Dinucleotide – a cofactor found in all living cells involved in redox reactions, carrying electrons from one reaction to another.
NICNAS	National Industrial Chemicals Notification and Assessment Scheme is the Australian government's regulatory body for industrial chemicals.
NIOSH	The National Institute for Occupational Safety and Health is the United States federal agency responsible for conducting research and making recommendations for the prevention of work-related injury and illness.
NOAEC	No Observed Adverse Effect Concentration.
$NOAEC_{LOCAL}$	No Observed Adverse Effect Concentration for local effect(s).
$NOAEC_{SYS}$	No Observed Adverse Effect Concentration for systemic effect(s).
NOAEL	No Observed Adverse Effect Level.
NTP	National Toxicology Program, US Department of Health and Human Services.
OECD	Organisation for Economic Co-operation and Development.
OEL	Occupational Exposure Limit (equivalent to a WES).

TERM	MEANING
Odds Ratio; OR	An odds ratio is a measure of association between an exposure and an outcome – the odds that an outcome will occur given a particular exposure, compared to the odds of the exposure occurring in the absence of that exposure.
OSHA	Occupational Safety and Health Administration, US Department of Labor.
PBPK/PB-PK	Physiologically based pharmacokinetic: a modelling technique for predicting the absorption, distribution, metabolism and excretion [ADME] of substances in humans and other animal species.
pp/PP	Post-partum.
ppm	Parts of vapour or gas per million parts of air.
RAR	Risk Assessment Report.
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals. An EU program and regulation.
RoC/ROC	Report on Carcinogens.
rsen	A substance that can 'sensitise' the respiratory system, inducing a state of hypersensitivity to it, so that on subsequent exposures, an allergic reaction can occur (which would not develop in non-sensitised individuals). It is uncommon to become sensitised to a compound after just a single reaction to it. A WorkSafe term.
RSEN	A notation indicating the substance is a respiratory sensitiser. RSEN is used in place of SEN when specific evidence of sensitisation by the inhalation route is confirmed by human or animal data. An ACGIH® term.
"S"	DFG MAK designation: *danger of sensitisation of the skin*.
S9/S-9	Supernatant fraction obtained from an organ (usually liver) homogenate by centrifuging at 9000g for 20 minutes in a suitable medium; this fraction contains cytosol and microsomes. The microsomes component of the S9 fraction contain cytochrome P450 isoforms (phase I metabolism) and other enzyme activities. The cytosolic portion contains the major part of the activities of transferases (phase II metabolism). The S9 fraction is used in assays to observe the effect of metabolism of drugs and other xenobiotics on the assay endpoint(s).
SCE	Sister Chromatid Exchange.
SCHER	Scientific Committee on Health and Environmental Risks.
SCOEL	The Scientific Committee on Occupational Exposure Limits is a committee of the European Commission, established in 1995 to advise on occupational health limits for chemicals in the workplace within the framework of Directive 98/24/EC, the chemical agents directive, and Directive 90/394/EEC, the carcinogens at work directive.
sen	A substance that can 'sensitise' the skin or respiratory system, inducing a state of hypersensitivity to it, so that on subsequent exposures, an allergic reaction can occur (which would not develop in non-sensitised individuals). It is uncommon to become sensitised to a compound after just a single reaction to it. A WorkSafe term.
SEN	A notation indicating the substance is a sensitiser. DSEN and RSEN are used in place of SEN when specific evidence of sensitisation by the dermal or respiratory route, respectively, is confirmed by human or animal data. An ACGIH® term.
SI	Stimulation Index.
skin	Skin absorption – applicable to a substance that is capable of being significantly absorbed into the body through contact with the skin. A WorkSafe term.
Skin	A notation indicating the potential for significant contribution to the overall exposure, by the cutaneous route, including mucous membranes and the eyes, by contact with vapours, liquids and solids. An ACGIH® term.
STEL	Short-Term Exposure Limit. The STEL is a limit value above which exposure should not occur and usually relates to a 15-minute reference period.
TG	Test Guidelines. An OECD term.

TERM	MEANING
TLV®	Threshold Limit Value (see TLV-STEL and TLV-TWA below). An ACGIH® term. Please see the Statement of Position Regarding the TLVs® and BEIs® and Policy Statement on the Uses of TLVs® and BEIs®
TLV-STEL	TLV-Short-Term Exposure Limit; a 15 minute TWA exposure that should not be exceeded at any time during a work day, even if the 8-hour TWA is within the TLV-TWA. An ACGIH® term.
TLV-TWA	TLV – Time-Weighted Average; the TWA concentration for a conventional 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed to, day after day, for a working lifetime without adverse effect. An ACGIH® term.
VA	Vinyl acetate.
v/v	Concentration, volume by volume.
WES	Workplace Exposure Standard – WESs are values that refer to the airborne concentration of substances, at which it is believed that nearly all workers can be repeatedly exposed to, day after day, without coming to harm. The values are normally calculated on work schedules of five shifts of eight hours duration over a 40 hour week. A WorkSafe term.
WES-STEL	The 15-minute time-weighted average exposure standard. Applies to any 15-minute period in the working day and is designed to protect the worker against adverse effects of irritation, chronic or irreversible tissue change, or narcosis that may increase the likelihood of accidents. The WES-STEL is not an alternative to the WES-TWA; both the short-term and time-weighted average exposures apply. Exposures at concentrations between the WES-TWA and the WES-STEL should be less than 15 minutes, should occur no more than four times per day, and there should be at least 60 minutes between successive exposures in this range.
WES-TWA	The average airborne concentration of a substance calculated over an eight-hour working day. A WorkSafe term.

Appendix 2: HSNO health-related hazardous substance classifications

This is the full list of all health-related hazardous substances classifications that are listed by the NZ EPA, including those that apply to this substance.

CLASSIFICATION CODE	MEANING
Acutely toxic	
6.1A	Substances that are acutely toxic – Fatal
6.1B	Substances that are acutely toxic – Fatal
6.1C	Substances that are acutely toxic – Toxic
6.1D	Substances that are acutely toxic – Harmful
6.1E	Substances that are acutely toxic – May be harmful, aspiration hazard
Skin irritant	
6.3A	Substances that are irritating to the skin
6.3B	Substances that are mildly irritating to the skin
Eye irritant	
6.4A	Substances that are irritating to the eye
Sensitisation	
6.5A	Substances that are respiratory sensitisers
6.5B	Substances that are contact sensitisers
Mutagens	
6.6A	Substances that are known or presumed human mutagens
6.6B	Substances that are suspected human mutagens
Carcinogens	
6.7A	Substances that are known or presumed human carcinogens
6.7B	Substances that are suspected human carcinogens
Reproductive/developmental toxicants	
6.8A	Substances that are known or presumed human reproductive or developmental toxicants
6.8B	Substances that are suspected human reproductive or developmental toxicants
6.8C	Substances that produce toxic human reproductive or developmental effects on or via lactation
Target organ toxicants	
6.9A	Substances that are toxic to human target organs or systems
6.9B	Substances that are harmful to human target organs or systems
Skin corrosive	
8.2A	Substances that are corrosive to dermal tissue (UN PGI)
8.2B	Substances that are corrosive to dermal tissue (UN PGII)
8.2C	Substances that are corrosive to dermal tissue (UN PGIII)
Eye corrosive	
8.3A	Substances that are corrosive to ocular tissue

Source: www.epa.govt.nz/industry-areas/hazardous-substances/rules-for-hazardous-substances/hazardous-substances-classification-codes

Appendix 3: References

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