Vinyl acetate; CASRN 108-05-4

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Vinyl acetate

File First On-Line 10/01/1990

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	yes	10/01/1990
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Vinyl acetate
CASRN — 108-05-4

Not available at this time.

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Vinyl acetate
CASRN — 108-05-4
Last Revised — 10/01/1990

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. Inhalation RfC Summary

Critical Effect	Exposures*	UF	MF	RfC
Nasal epithelial lesions **Chronic inhalation study in rats and mice** **Owen, 1988; Beems, 1988; Dreef-van der Meulen, 1988**	NOAEL: 176 mg/cu.m (50 ppm) NOAEL(ADJ): 31 mg/cu.m NOAEL(HEC): 5 mg/cu.m LOAEL: 704 mg/cu.m (200 ppm) LOAEL(ADJ): 126 mg/cu.m LOAEL(HEC): 19 mg/cu.m	30	1	2E-1 mg/cu.m

*Conversion Factors: MW=86.09. Assuming 25C and 760 mmHg, NOAEL(mg/cu.m) = NOAEL(ppm) x MW/24.45 = 176. NOAEL(ADJ)= 176 mg/cu.m x (6 hour/24 hour) x (5 days/7 days) = 31 mg/cu.m. The NOAEL(HEC) was calculated for a gas: respiratory effect in the ExtraThoracic region for females of both species. For rats, MVa = 0.20 cu.m/day, MVh = 20.0 cu.m/day, Sa(ET) = 11.6 sq. cm, Sh(ET) = 177 sq. cm. RGDR(ET) = (MVa/Sa)/(MVh/Sh) = 0.15. NOAEL(HEC) = NOAEL(ADJ) x RGDR = 5 mg/cu.m. For mice, MVa = 0.05 cu.m/day,

MVh = 20 cu.m/day, Sa(ET) = 2.9 sq. cm, Sh(ET) = 177 sq.cm. RGDR(ET) = (MVa/Sa) / (MVh/Sh) = 0.15. NOAEL(HEC) = NOAEL(ADJ) x RGDR = 5 mg/cu.m.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

The principal study of Owen (1988) comprises the pathology reports on Owen's animals done by Beems (1988) and Dreef-van der Meulen (1988).

Owen, P.E. 1988. Vinyl acetate: 104 week inhalation combined chronic toxicity and carcinogenicity study in the rat and mouse. Report prepared by Hazleton Laboratories Europe Ltd., Harrogate, England for the Society of the Plastics Industry, Inc., New York. Report No.: 5547-51/15. November 1988.

Dreef-van der Meulen, H.C. 1988. Report No. V 88.033/270836: Histopathology of the respiratory tract of rats used in a 104 week inhalation study (Owen, 1988) with vinyl acetate: Revised version. (TNO-CIVO Institutes, October 1988).

Beems, R.B. 1988. Report No. V 88.133: Histopathology of the respiratory tract of mice used in a 104-week inhalation study (Owen, 1988) with vinyl acetate. (TNO-CIVO Institutes, April 1988).

Sprague-Dawley rats (Crl:CD[SD]BR) and mice (Crl:CD-1[ICR]BR) (90 animals/sex/dose, 60 for the main study and 30 for laboratory testing, interim sacrifices at 51 and 81 weeks and recovery) were exposed to 0, 50, 200, or 600 ppm of 99.9% vinyl acetate (VA) for 6 hours/day, 5 days/week for 104 weeks. These values correspond to 0, 176, 704, and 2113 mg/cu.m, and when duration- adjusted become 0, 31, 126, and 378 mg/cu.m. Chamber concentrations were determined with GC every 15 minutes throughout the exposure day. Analysis for acetaldehyde, a hydrolysis product of VA, was determined at monthly intervals in the high-dose chamber, the mean concentration in the test chamber being 49 ppm (89 mg/cu.m, duration-adjusted to 16 mg/cu.m). Histology was performed on all principal organs (including trachea and testes) with special attention given to lungs (all 5 lobes sectioned longitudinally) and the nasal turbinates (sectioned into 6 levels). Exposure to VA vapors did not influence overall survival to study termination in either rats or mice. Rough haircoat and hunched posture were seen in both species at all concentrations and were associated with exposure, although no incidences are given.

In rats exposed to the high concentration of VA (600 ppm), Owen (1988) noted lesions at different levels in the respiratory tract. In the histopathology report of Dreef-van der Meulen (1988) on Owen's animals, olfactory epithelial metaplasia/atrophy and nest-like epithelial folds (hyperplastic, regenerative epithelial structures) were noted in the nasal cavity, exfoliation of bronchial epithelium, fibrous intraluminal projections (also termed tags, indicative of

regeneration of exfoliated areas) in the bronchi, and pigmented histiocyte accumulation in the lungs. No alterations were noted in the trachea. Data presented in the study showed that these respiratory tract lesions all occurred in the high-exposure animals with increased severity or at incidences significantly greater than in controls ($p<0.05$ to $p<0.001$). Body weight gain was reduced significantly only in this group (15% in both females and males). At termination of the experiment, decreases were observed in absolute and/or relative weights in the high-dose animals for a number of organs in both sexes including brain, lung, liver, heart, kidneys, thyroid, and spleen (but not testes) although there was nothing remarkable in the histopathology or clinical chemistry to corroborate these alterations.

In the nasal cavity of rats exposed to 200 ppm VA there was clear evidence of atrophy (judged slight in 70 of 120 animals, both sexes) and metaplasia (judged very slight in 5 of 60 female rats) in the olfactory epithelia. Nasal basal cell hyperplasia (judged slight or moderate in 78 of 119 animals of both sexes) was also noted. No lesions were noted in the nasal cavities of low-dose (50 ppm) animals that were different from controls or related to exposure in a concentration-dependent manner. In the rats subjected to mid (200 ppm) and low (50 ppm) exposures, lesions observed in the lungs, bronchi, or trachea were not different in incidence or severity from controls. An exposure-related gradation of overall effects was apparent; the high (600 ppm) exposure affecting the entire animal, the mid (200 ppm) involving only the nasal cavity and the low exposure (50 ppm) being a no effect level. Thus, the nasal cavity (the extrathoracic region) is considered as the affected region for this chemical. Based on the lesions in the nasal cavity, the mid range exposure of 200 ppm (HEC = 19 mg/cu.m) is designated the LOAEL; the lowest dose level of 50 ppm (HEC = 5 mg/cu.m) is designated the NOAEL.

Owen (1988) also noted respiratory tract lesions in mice exposed for the same duration to the same high concentration (600 ppm) as the rats. In the histopathology report of the Owen study (by Beems, 1988) replacement of olfactory by respiratory epithelium, atrophy of olfactory epithelium (other than in the dorsal meatus) and submucosal gland hyperplasia was observed in the nasal cavity of both sexes at the mid two highest exposure concentrations (200 and 600 ppm) in a dose-dependent manner for severity and incidence. Although not affected in rats, epithelial hyperplasia was noted in the trachei of 2/51 200-ppm and 19/48 600-ppm exposure males and in 11/48 600-ppm exposed females. Very slight to severe exfoliation/epithelial flattening of bronchial epithelium was noted only in high-dose animals. Fibrous intraluminal projections (tags) were present in the bronchi of both sexes but only in the high-dose animals. Body weight gain was reduced in the highest (15% for females, 10% for males) and in the 200-ppm exposure groups (percent not listed). At the termination of the experiment, significant weight alterations were observed in several organs, including increases in relative brain and lung weights (both sexes) and decreases in absolute liver, heart, and kidney weights. There was no accompanying pathology in any of these tissues, except there was increased incidence of pigmented histiocyte accumulation in the lungs of the 600-ppm exposure group.

In the lungs of low-dose mice, the incidence of pigmented histiocyte accumulation was not different from controls. No lesions were noted in the trachei of either controls or low-dose animals. No lesions were noted in the nasal cavities of low-dose animals that were different from controls. An exposure-related gradation of overall effects was apparent: the high-range exposure affected the entire animal, the mid range involved only the nasal cavity, and the low range a no effect level. Thus, the nasal cavity (the extrathoracic region) is considered the affected region for this chemical. 200 ppm (HEC = 20 mg/cu.m) is designated the LOAEL for consideration of histopathologic lesions in the trachea and nasal cavity; the lowest dose level of 50 ppm (HEC = 5 mg/cu.m), which showed none of these lesions, is designated the NOAEL. The values derived from female animals were used as they were slightly lower and therefore more conservative.

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF — An uncertainty factor of 10 is used for protection of sensitive human subpopulations. An uncertainty factor of 3 for interspecies variability is used because the use of the dosimetric adjustments account for part of this area of uncertainty.

MF — None

I.B.4. Additional Studies/Comments (Inhalation RfC)

Acetaldehyde is a hydrolysis product of vinyl acetate and is itself an irritant. Levels of acetaldehyde in the high exposure chamber of the Owen (1988) study were 49 ppm (89 mg/cu.m, duration adjusted = 16 mg/cu.m of a total 378 mg/cu.m VA). The reference concentration for acetaldehyde has been verified based on histopathological changes in the respiratory tract in rats with a LOAEL(ADJ) of 130 mg/cu.m. The study of Appleman et al. (1986) indicated a NOAEL(ADJ) of 48.75 mg/cu.m although this study was only 4 weeks in duration. Based on these facts, it is unlikely that the respiratory effects observed in the Owen (1988) study could be caused by this contaminant at the levels at which it was present in the chambers.

In an occupational study by Deese and Joyner (1969), no adverse effects associated with long-term occupational exposure were detected in a review of medical records and the results of multiphasic examinations (as judged by chest x-rays, blood chemistry, electrocardiogram, and urinalysis) for workers in three vinyl acetate production units of a chemical plant. The mean concentration of vinyl acetate in the air in the vinyl acetate production units was 8.6 ppm based on a range of 0 to 49.3 ppm. Time-weighted average exposures of 8.2, 5.2, and 7.7 ppm were calculated for the three production units. The possibility of occasional exposure to higher levels was noted with concentrations as high as 326.5 ppm measured for some operations. A cohort of 21 chemical operators with a mean length of employment of 15.2 years in the vinyl acetate complex volunteered for the study. The control group was composed of workers from other

production units who had never worked in the vinyl acetate complex. There was no indication whether or not statistical analysis was performed. As this is an occupational study, MVho = 10 cu.m./day, MVh = 20 cu.m./day, NOAEL(ADJ) = 29 x MVho/MVh x 5/7 days = a free- standing NOAEL(HEC) of 10 mg/cu.m.

Subjective descriptions of VA irritancy and approximate levels at which these effects occurred were noted in a limited study of vinyl acetate exposure in humans (n=3 to 5) conducted and reported by Deese and Joiner (1969) as part of the above discussed epidemiological study. Three of three subjects considered exposure to VA at 21.6 ppm (76 mg/cu.m) "for an extended time" (which was not indicated) to be intolerable due to eye irritation. Upper respiratory irritation (as indicated by hoarseness and coughing) was also noted at 21.6 ppm by a "majority" of 3 to 5 subjects. Both eye irritation and upper respiratory irritation was reported by one of three subjects exposed to 4.2 to 6.8 ppm (15 to 24 mg/cu.m). Three of three subjects detected a slight odor of VA when exposed to 0.4 ppm (1.4 mg/cu.m).

Mice (10 animals/sex/concentration, CD-1 strain) were exposed to 99.9% vinyl acetate (VA) vapor at concentrations of 0, 50, 200, or 1000 ppm (0, 176, 704, 3520 mg/cu.m) 6 hours/day, 5 days/week for 13 weeks (Owen, 1980a). The duration-adjusted concentrations for these values are 0, 31, 126, or 629 mg/cu.m. Chamber concentrations were determined every 15 minutes throughout the experimental day by GC analysis. Histology was performed in all exposure groups on all principal organs with special attention given to the turbinates (two levels), lungs (three lobes) and trachea (three levels). Histopathology revealed VA-related effects at all levels of the respiratory tract but predominately in the tissues of the high-dose animals. The only lesions appearing to follow a dose-response at 200 ppm were focal pneumonitis in the lung (2/20 vs 4/20 in the high exposure, no incidence in controls or low exposure) and diffuse rhinitis in the nasal cavity (3/20 in mid vs 11/20 in the high exposure, 1/20 in both low exposure and controls). No epithelial atrophy or regeneration was reported in this study. The observed lesions are similar to those induced by respiratory pathogens although the lack of these lesions in the controls does not favor a pathogenic etiology. Based on focal pneumonitis in the lung and diffuse rhinitis in the nasal cavity, the mid exposure (200 ppm) is designated as the LOAEL in this study with the affected region being the total respiratory tract. This decision is reinforced by interim sacrifices of the chronic study at weeks 53 and 83 (Owen, 1988) which also showed lesions in the nasal epithelia; focal pneumonitis and rhinitis at week 13 may be precursors to these pathologies. The low exposure level of 50 ppm is designated as the NOAEL for this study. Although the total respiratory system may be involved, the NOAEL(HEC) for this study was calculated for a gas:respiratory effect in the extrathoracic region as this procedure gives a more conservative value, NOAEL(HEC) = 5 mg/cu.m.

Owen (1980b) exposed rats (10 animals/sex/concentration, Sprague-Dawley, CD strain) to vinyl acetate vapors (99.9%) under conditions and experimental parameters identical to those used in

mice (Owen, 1980a). Body weight gain was reduced significantly (20% relative to controls at end of study) in both males and females exposed to the high dose (1000 ppm). After 12 weeks of treatment there was moderate ($p<0.05$) increase in hemoglobin volume in high dose males only. No treatment-related lesions were detected by macroscopic or microscopic examination (including testes and lungs) with the exception of animals exposed to 1000 ppm in which the incidence of focal histiocytic alveolitis increased mildly from 9/20 in controls to 19/20 in high-dose animals (no degree of severity given). A LOAEL based on weight loss in the high dose (629-mg/cu.m) group is identified in this study. The NOAEL(HEC) is based on a gas:extrarespiratory scenario in which periodicity was assumed to have been attained. As the blood:air partition coefficients are unknown for both animals and humans a default value of 1 is used; NOAEL(HEC) = 126 mg/cu.m x 1 = 126 mg/cu.m.

In the developmental study by Irvine (1980) rats (24 mated females/ concentration) were exposed to 0, 52, 198, or 1004 ppm 99.9% VA on gestation days 6 through 15 for 6 hours/day (0, 182, 696, or 3533 mg/cu.m., not duration-adjusted). Chamber concentrations of VA were checked every 15 minutes during the exposure period. Analysis for acetaldehyde was determined once in the high-dose chamber and was found to be 32 mg/cu.m (total VA = 3533 mg/cu.m). No deaths occurred during the study and no treatment-related clinical signs were observed. The 1004-ppm exposure was toxic to the dams, as average body weight gain was 10 to 12% lower than the controls from day 10 of gestation to the day of sacrifice; body weight gains observed in the mid (198 ppm) and low (52 ppm) exposure groups were not different from the controls at any time during the experimental period. Neither the pregnancy incidence (range 92 to 100%), the incidence of pre- and post-implantation losses, nor the mean number of corpora lutea/dam (range 16.1 to 16.5) was different between the control and the treated groups. Growth retardation was present in the fetuses of dams exposed to the level of VA that also elicited maternal growth retardation (1004 ppm); decreased mean litter weight, mean fetal weight, and mean fetal crown/rump length ($p >0.01$ for all these parameters) was observed. A significant ($p<0.01$) increase in incidence of retardation of sternebral and occipital ossification was observed in the fetuses of animals exposed to 1004 ppm, but not in the other exposure groups. Thus inhalation exposure of VA up to levels that were maternally toxic did not produce embryolethality or teratogenicity. Fetal growth retardation did occur but only in embryos from the high exposure group and therefore in conjunction with maternal growth retardation. Based on the effects discussed previously, the non-adjusted exposure level of 3533 mg/cu.m is considered a LOAEL (HEC) with the next lowest level, 696 mg/cu.m designated the NOAEL(HEC).

In the study of Shaw (1987), groups of Crl:CD(SD)BR Sprague-Dawley rats were exposed (in drinking water) to 0, 200, 1000, or 5000 ppm VA (0, 30, 152, or 760 mg/kg/day for females, 0, 28, 139, or 693 mg/kg/day for males) in a 2- generation reproduction study. The parental (P) generation had 18 males and 36 females/group, the F1 generation 25 of each sex/group. The P animals were treated for 10 weeks prior to mating and, for females, treatment continued

throughout mating, gestation, and lactation. No effects on reproductive performance of the P animals were noted in any treatment group although there was a significant reduction in body weight gain of the high-dose F1a pups. Body weight gain was reduced by 8% in the 5000-ppm P females and in both 1000- ppm (9%) and 5000-ppm (11%) F1 females during lactation. No treatment-related effect was noted on the mating or gestation indices and no apparent effects were noted in pup numbers, functional tests, or developmental parameters in any treatment group. Results from the cross-mating phase (performed with controls and high-dose animals only) indicated a marginal effect (not statistically significant) on the reproductive performance of the males dosed at 5000 ppm. The study of Lahdetie (1988) demonstrates adverse testicular effects in response to an intraperitoneal injection of 500 mg/kg VA in mice. However, no macroscopic or microscopic abnormalities in the reproductive organs of the 5000 ppm F1 males in this study could be attributed to chemical exposure. Based on these results 693 mg/kg/day is considered a LOAEL with 139 mg/kg/day the NOAEL.

No data gaps exist for this compound.

I.B.5. Confidence in the Inhalation RfC

Study — High
Database — High
RfC -- High

The study by Owen (1988) identified both a NOAEL and a LOAEL for histopathology of the nasal olfactory epithelia in rats and in mice in a chronic 2-year study. The study used an adequate number of animals and was thorough in reporting experimental and exposure details. The animal database provides sufficient supporting data for the RfC. Confidence in the principal study and database is high. High confidence in the RfC follows.

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — None

Agency Work Group Review — 08/23/1990

Verification Date — 08/23/1990

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Vinyl acetate
CASRN — 108-05-4

Not available at this time.

VI. Bibliography

Sustance Name -- Vinyl acetate
CASRN — 108-05-4

VI.A. Oral RfD References

None

VI.B. Inhalation RfC References

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed., Cincinnati, OH. p. 621.

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Deese, D.E. and R.E. Joyner. 1969. Vinyl acetate: A study of chronic human exposure. Am. Ind. Hyg. Assoc. J. 30: 449-457.

Dreef-van der Meulen, H.C. 1988. Report No. V 88.033/270836: Histopathology of the respiratory tract of rats used in a 104 week inhalation study with vinylacetate: Revised version. (TNO-CIVO Institutes, October 1988)

Irvine, L.F.H. 1980. Vinyl acetate oral and inhalation teratology studies in the rat. Report prepared by Hazleton Laboratories Europe Ltd., Harrogate, England for the Society of the Plastics Industry, Inc., New York. Report No. 2195-51/6&7. October 1980

Lahdetie, J. 1988. Effects of vinyl acetate and acetaldehyde on sperm morphology and meiotic micronuclei in mice. Muta. Res. 202: 171-178.

Owen, P.E. 1980a. Vinyl acetate: 3 month inhalation toxicity study in the mouse. Report prepared by Hazleton Laboratories Europe Ltd., Harrogate, England for the Society of the Plastics Industry, Inc., New York. Report No. 2303-51/5. May 1980.

Owen, P.E. 1980b. Vinyl acetate: 3 month inhalation toxicity study in the rat. Report prepared by Hazleton Laboratories Europe Ltd., Harrogate, England for the Society of the Plastics Industry, Inc., New York. Report No. 2286- 51/5. May 1980. 249 p.

Owen, P.E. 1988. Vinyl acetate: 104 week inhalation combined chronic toxicity and carcinogenicity study in the rat and mouse. Report prepared by Hazleton Laboratories Europe Ltd., Harrogate, England for the Society of the Plastics Industry, Inc., New York. Report No. 5547-51/15. November 1988.

Shaw, D.C. 1987. Vinyl acetate: Oral (drinking water) 2 generation reproduction study in the rat. Report prepared by Hazleton Laboratories Europe Ltd., North Yorkshire, England, for the Society of Plastics Industry, Inc., NY,NY. Report No. 4661-51/17a. December 1987. 91 p.

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Vinyl acetate
CASRN — 108-05-4

Date	Section	Description
10/01/1990	I.B.	Inhalation RfC summary on-line

VIII. Synonyms

Substance Name — Vinyl acetate
CASRN — 108-05-4
Last Revised — 10/01/1990

- 108-05-4
- ACETATE DE VINYLE [FRENCH]
- ACETATO DE VINILO [SPANISH]
- ACETIC ACID ETHENYL ESTER
- ACETIC ACID, ETHENYL ESTER
- ACETIC ACID VINYL ESTER
- 1-ACETOXYETHYLENE
- ETHENYL ACETATE
- HSDB 190
- NSC 8404
- OCTAN WINYLU [POLISH]
- UN 1301
- VAC
- VINILE (ACETATO DI) [ITALIAN]
- VINYLACETAAT [DUTCH]
- VINYLACETAT [GERMAN]
- VINYL ACETATE
- VINYL ACETATE, INHIBITED
- VINYL A MONOMER
- VINYLE (ACETATE DE) [FRENCH]
- VINYLESTER KYSELINY OCTOVE [CZECH]
- VYAC