Screening Assessment for the Challenge

Acetic acid ethenyl ester
(Vinyl Acetate Monomer)

Chemical Abstracts Service Registry Number
108-05-4

Environment Canada
Health Canada

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Synopsis

Pursuant to section 74 of the *Canadian Environmental Protection Act*, *1999*, (CEPA 1999) the Ministers of the Environment and of Health have conducted a screening assessment of acetic acid ethenyl ester, otherwise commonly referred to as vinyl acetate, Chemical Abstracts Service Registry Number 108-05-4, a substance identified in the categorization of the Domestic Substances List as a high priority for action under the Ministerial Challenge. Vinyl acetate was identified as a high priority as it was considered to pose greatest potential for exposure to individuals in Canada and had been classified by other agencies on the basis of carcinogenicity. The substance did not meet the ecological categorization criterion for persistence, bioaccumulation or inherently toxic to aquatic organisms. Therefore, the focus of this assessment of vinyl acetate relates to human health aspects.

According to the data submitted in response to section 71 of CEPA 1999, vinyl acetate is primarily imported into Canada, between ten and fifty-thousand metric tons (2006 data), for use in the industrial synthesis of polyvinyl acetate (PVAc) and vinyl acetate (co)polymers such as ethylene vinyl acetate or EVA copolymer. These polymers are subsequently applied in the manufacturing of various types of products for industrial and consumer applications. Vinyl acetate monomer itself has no direct use as an end-use product nor is it added intentionally; it is only found as a residue of manufacturing polymerization processes. As PVAc is used to manufacture polyvinyl alcohols, polyvinyl alcohols do not contain any residues of vinyl acetate monomer. Consumer products that may contain residues of vinyl acetate monomer include adhesives, joint sealants, caulks, latex paints, plasters, food packaging (including films) and cosmetics. Synthesized polymers, including emulsion dispersions, may undergo devolatilization processes to further reduce any trace residual amounts of monomer that remain. Such residual exposures constitute “direct” exposures whereas, “indirect” exposures occur from industrial releases during manufacturing, processing, storage and transport. The industrial releases occur primarily to ambient air as a result of vinyl acetate’s vapour pressure. In ambient air, the monomer may be degraded by free-radical hydroxylation or by ozonation. Vinyl acetate tends to remain in the environmental media to which it is released.

Based principally on the weight of evidence assessment of the International Agency for Research on Cancer and the European Union,a critical effect for characterization of risk to human health for vinyl acetate is carcinogenicity. Tumours of the nasal cavity in male and female rats were observed following inhalation exposure to vinyl acetate at the highest dose tested. More recent studies also reported squamous cell carcinomas of the upper digestive tract in both sexes of mice and rats following oral exposure to vinyl acetate. Vinyl acetate was also found to produce DNA-protein crosslinks and is genotoxic (clastogenic) in human cells *in vitro* and in animals *in vivo*, effects considered secondary to the metabolism of vinyl acetate to acetaldehyde, a known crosslinker.

The margins of exposure based on non-neoplastic effects (effects of the upper respiratory tract in animals and humans) and the upper bounding estimates of exposure to the general population derived from environmental media and consumer products are adequate to account for uncertainties in the databases on exposure and effects.

On the basis of the consideration of the existence of a practical threshold for carcinogenicity of vinyl acetate in the animal studies, considering the magnitude of the margins of exposure for effects, it is proposed that vinyl acetate be considered as a substance that is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

On the basis of ecological hazard and reported releases of vinyl acetate, it is proposed that this substance is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity, or that constitute or may constitute a danger to the environment on which life depends. Vinyl acetate does not meet the criterion for persistence and bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations*.

Based on the information available, it is concluded that vinyl acetate monomer does not meet any of the criteria set out in section 64 of CEPA 1999.

Introduction

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) (Canada 1999) requires the Minister of the Environment and the Minister of Health to conduct screening assessments of substances that have met the categorization criteria set out in the Act to determine whether these substances present or may present a risk to the environment or human health. Based on the results of a screening assessment, the Ministers can propose to take no further action with respect to the substance, to add the substance to the Priority Substances List (PSL) for further assessment, or to recommend that the substance be added to the List of Toxic Substances in Schedule 1 of the Act and, where applicable, the implementation of virtual elimination.

Based on the information obtained through the categorization process, the Ministers identified a number of substances as high priorities for action. These include substances that

- met all of the ecological categorization criteria, including persistence (P), bioaccumulation potential (B) and inherent toxicity to aquatic organisms (iT), and were believed to be in commerce; and/or
- met the categorization criteria for greatest potential for exposure (GPE) or presented an intermediate potential for exposure (IPE), and had been identified as posing a high hazard to human health based on classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity or reproductive toxicity.

The Ministers therefore published a notice of intent in the *Canada Gazette*, Part I, on December 9, 2006 (Canada 2006), that challenged industry and other interested stakeholders to submit, within specified timelines, specific information that may be used to inform risk assessment, and to develop and benchmark best practices for the risk management and product stewardship of those substances identified as high priorities.

The substance, vinyl acetate (monomer) was identified as a high priority for assessment of human health risk because it was considered to be present [GPE] and had been classified by other agencies on the basis of carcinogenicity. The Challenge for vinyl acetate (monomer) was published in the *Canada Gazette* on May 12, 2007 (Canada 2007). A substance profile was released at the same time. The substance profile presented the technical information available prior to December 2005 that formed the basis for categorization of this substance. As a result of the Challenge, submissions of information were received.

Although vinyl acetate was determined to be a high priority for assessment with respect to human health, it did not meet the criteria for potential for persistence, bioaccumulation and inherent toxicity for aquatic organisms. Therefore, this assessment focuses principally on information relevant to the evaluation of risks to human health.

Under CEPA 1999, screening assessments focus on information critical to determining whether a substance meets the criteria for defining a chemical as toxic as set out in section 64 of the Act, where

> "64. […] a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions that

(*a*) have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
(*b*) constitute or may constitute a danger to the environment on which life depends; or
(*c*) constitute or may constitute a danger in Canada to human life or health."

Screening assessments examine scientific information and develop conclusions by incorporating a weight of evidence approach and precaution.

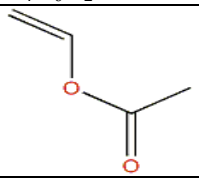
This screening assessment includes consideration of information on chemical properties, hazards, uses and exposure, including the additional information submitted under the Challenge. Data relevant to the screening assessment of this substance were identified in original literature, review and assessment documents, stakeholder research reports and from recent literature searches, up to July 2007 for health effects and exposure. Key studies were critically evaluated; modelling results may have been used to reach conclusions.

Evaluation of risk to human health involves consideration of data relevant to estimation of exposure (non-occupational) of the general population, as well as information on health hazards (based principally on the weight of evidence assessments of other agencies that were used for prioritization the substance). Decisions for human health are based on the nature of the critical effect and/or margins between conservative effect levels and estimates of exposure, taking into account confidence in the completeness of the identified databases on both exposure and effects, within a screening context. The screening assessment does not represent and exhaustive or critical review of all available data. Rather, it presents a summary of the critical information upon which the conclusion is based.

This screening assessment was prepared by staff in the Existing Substances Programs at Health Canada and Environment Canada and incorporates input from other programs within these departments. This assessment has undergone external written peer review/consultation. Comments on the technical portions relevant to human health were received from scientific experts selected and directed by Toxicology Excellence for Risk Assessment (TERA), including Dr. Michael Jayjock (The LifeLine Group), Dr. Katherine Walker (Independent Consultant), and Dr. Susan Griffin (U.S. Environmental Protection Agency). While external comments were taken into consideration, the final content and outcome of the screening risk assessment remain the responsibility of Health Canada and Environment Canada. Additionally, the draft of this screening assessment was subject to a 60-day public comment period. The critical information and considerations upon which the assessment is based are summarized below.

Substance Identity

Table 1 Substance Identity

CAS RN	108-05-4
Chemical DSL name	Acetic acid ethenyl ester
Synonyms	Acetic acid vinyl ester, vinyl acetate monomer or VAM, vinyl acetate, ethenyl acetate, 1-acetoxyethylene, acetoxyethene, acetoxyethylene, NSC 8404, Ponal, UN 1301, UN 1301 (DOT)
Molecular formula	$C_4H_6O_2$
Chemical structure	
Molecular weight	86.1 g/mol

Physical Chemical Properties

Physical state and characteristics: Vinyl acetate is a colorless, flammable liquid at room temperature (20ºC). As the monomer is an organic ester, it has a sweet smell in small quantities. Being an organic ester, vinyl acetate monomer is soluble in many organic solvents of varying solvent strength such as ethane, acetone and chloroform. In the presence of light, the monomer will initiate self-polymerization (HSDB, 1991).

Table 2: Physical/Chemical Properties

Property	Type	Value	Rating	Reference
Melting Point (°C)	Experimental	-93.2		Lide 1995-1996;
Boiling Point (°C)	Experimental	72.7		Budavari 1996; Ullmann 1995
Density (g/cm^3)	Experimental	0.932 (20°C)		Budavari 1996;
Water solubility (mg/L)	Experimental	$2x10^4$ (20°C)	very high	Riddick and Bunger 1986
Vapour Pressure (mm Hg)	Experimental	89.1 (20 ºC)	very high	Vinyl Acetate Council 2003
Henry's Law constant, K_H (atm·m^3/mol)	Experimental	$4.81x10^{-4}$		Verschueren 1983
Log K_H	Estimated	-3.31	moderate	Calculated from K_H
Log Kow	Experimental	0.7	low	Hansch et al. 1995
Log Koc	Modelled	0.788-1.78	very low	PCKOCWIN v1.66 2000 HSDB 1991

Sources

Sources of human exposure to vinyl acetate in Canada may either be from point sources releases such as those associated with industrial sites of manufacturing or processing whereas, non-point sources would encompass those releases from commercial or industrial products within the Canadian marketplace e.g. by off-gasing or migration.

In Canada, the sole Canadian producer of vinyl acetate in significant quantities, Celanese Canada, operated between 1979 to its closure in early 2002 with an annual capacity < 100,000 metric tons. The two established major commercial processes for the manufacturing of vinyl acetate monomer include the ethylene process and the acetylene process. The Canadian plant was closed upon expansion of its businesses into other foreign global markets (SRI Consulting, 2004). Vinyl acetate monomer was manufactured < 100 kg in 2006 (Environment Canada 2007). Currently, almost all of raw vinyl acetate monomer precursor is imported into Canada for the manufacturing of (co)polymers and formulated end-products.

Homo- and (co)polymers of vinyl esters are produced both in the homogeneous phase either by bulk or solution polymerization and in the heterogeneous phase, by suspension and emulsion polymerization. The combination of high reactivity of the vinyl acetate radical species coupled with the low reactivity of vinyl acetate towards attack by radicals results in high chain-transfer constants of vinyl acetate, poly(vinyl acetate) and other polymers relative to the vinyl acetate radical or the growing chain. This contributes to low or nondetectable residues of vinyl acetate in synthesized products. Emulsion polymerization is the most important synthesis process as it is used primarily to manufacture a variety of product types including paints, adhesives, binders for non-woven fabrics, synthetic rubbers, additives in paper and textiles, leather-treatment materials, impact modifiers for plastic matrices, and additives for construction materials (Ullmann 1995).

Uses

In Canada, all of vinyl acetate monomer is used for industrial synthesis applications of either polyvinyl acetate(PVAc) or (co)polymers for use in formulations of industrial and consumer products. There are no direct consumer end-use products of vinyl acetate monomer itself; vinyl acetate monomer may be found in products as residuals from the polymerization process. Products include water-borne dispersion latex paints, universal wood glues, solid stick hot melt adhesives for glue guns, food product packaging from packaging adhesives, caulks, plasters, cosmetics and plastic products and pesticides. Vinyl acetate may also be used as a fuel additive. In cosmetics and personal care products it operates as a film former and is found in several hair grooming products, eye makeup preparations and in one nail polish product in Canada. Vinyl acetate is neither a prohibited or restricted cosmetic ingredient (Health Canada, 2007). For pesticides, vinyl acetate is a list 2 formulant at 0.009-1.75% where it functions as a binder, sticker or spreader (unpublished data provided by Pest Management Regulatory Agency, Health Canada 2008a).

In Canada, ethylene vinyl acetate (co)polymers and poly(vinyl acetate) (homo)polymer derived plastics are approved food contact plastics (Health Canada 2008b). Adhesives containing vinyl acetate are applied to food packaging cover seams and surfaces and thus rarely come into direct contact with foods. In Canada, vinyl acetate is not classified as a food additive (Division 16 of the *Food and Drugs Regulations)* (Justice Canada, 2008).

Releases to the Environment

Based on reported releases to the NPRI, the majority of vinyl acetate releases to the environment occur to ambient air. Emission point sources in Alberta account for 90% of total releases to ambient air (NPRI, 2008).

Table 3: NPRI Data [1]

Year	On-Site Releases (tonnes)				Disposal (tonnes)	
	Air	Water	Land	Total	On-Site	Off-Site
2006	110	0	1.25	113	0	96
2005	135	0	1.19	138	0	135
2004	128	0	1.14	130	0	96

[1] some values were rounded

Environmental Fate

Vinyl acetate is expected to partition predominantly to the compartment to which it is released. Hydrolysis of vinyl acetate in natural water occurs in 7 days (Mill and Mabey 1978, 1985). The estimated K_{oc} of 0.788 suggests that it is not expected to adsorb to sediments and suspended solids in water. In air, vinyl acetate is highly volatile and undergoes atmospheric degradation in 0.41 – 0.43 days (Atkinson 1989). Ozonation also is likely with a half-life of 3.6 – 6.5 days (Atkinson 1989; AOPWIN v1.91, 2000). In soil, the K_{oc} value of 0.788 suggests a high mobility in soil. The aqueous hydrolysis half-life of 7.3 days indicates that hydrolysis should be a significant process for the substance in moist soils (HSDB 2005). Volatilization from dry and wet soils seems to be an important fate process based on its vapour pressure and Henry's Law constant (HENRYWIN v.3.10, 2000).

Table 4: Results of the Equilibrium Criterion EQC Level III modelling (EQC v.2.02, 2003)

	Fraction of Substance Partitioning to Each Medium (%)			
Substance released to:	**% in Air**	**% in Water**	**% in Soil**	**% in Sediment**
-Air (100%)	96.2	3.54	0.26	6.2×10^{-3}
-Water (100%)	2.09	97.7	5.7×10^{-3}	0.17
- Soil (100%)	6.22	12.6	81.2	0.022
- Air, water, soil (33% each)	6.94	61.7	31.2	0.11

Persistence and Bioaccumulation Potential

Environmental Persistence

Partitioning of vinyl acetate occurs mainly in water and soil (93%). Vinyl acetate degrades rapidly in the atmosphere (half-life of 0.43 days). Short half lives in air of 3.5-6.5 days suggest that it is not persistent in air. In water, experimental hydrolysis data of a half-life of 7.3 days indicates that vinyl acetate is not considered to be persistent in water based on the half-life criteria of $\geq$ 6 months in water/soil as specified in the *Persistence and Bioaccumulation Regulations* (Canada 2000). Biodegradation rates of 82-98% vinyl acetate (initial concentration of 100 mg/L) was measured as

BOD over a 14 day test period in the Modified MITI test using an activated sludge inoculum (MITI 1992; NITE 1992). The estimated timeframe and probability for biodegradation indicates that vinyl acetate remains in water ≤ 182 days. The half-life in soils is expected to be ≤ 182 days. For sediment, half-life is thus expected to be four times higher (i.e., ≤60 days). Vinyl acetate is not expected to be persistent in soil and sediment.

Table 5: Experimental and modelled persistence values for vinyl acetate

Experimental				
Medium	**Fate Process**	**Degradation Value**	**Endpoint/Units**	**Reference**
Air	Atm. Oxidation (O_3) / (OH)	3.5/0.4	Half-life, days	Atkinson 1989
Water	Hydrolysis	7.3	Half-life, days	Mill and Mabey 1978
Water	Biodegradation	82-98	% Biodegradation	NITE 1992
Soil	Biodegradation	26	Hours	Nieder et al. 1990
Sewage	Biodegradation	7.5	Hours	Nieder et al. 1990
Sludge	Biodegradation	5.0	Hours	Nieder et al. 1990
Modelled				
Air	Atm. Oxidation (OH)/ Ozone reaction	0.4 /6.5	Half-life, days (12 hour)	AOPWIN v1.91 2000
Water/Soil	Biodegradation	15	Half-life, days	BIOWIN v4.02 Ultimate survey, 2000
Water/Soil	Biodegradation	0.88- 0.99	Probability	BIOWIN v4.02, 2000
Water	Hydrolysis	141.6	Half-life, days	HYDROWIN v1.67, 2000
Soil/ Sediment	Degradation	15/60	Half-life, days	Boethling et al. 1995

The weight of evidence based on the above-described data indicates that vinyl acetate does not meet the persistence criteria for air (half life in air ≥ 2 days) and/or water and/or soil (half life in soil and water ≥ 182 days) and/or sediments (half life in soil and water ≥ 365 days) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Potential for Bioaccumulation

Table 6 shows the weight of evidence indicates that vinyl acetate does not meet the bioaccumulation criterion (BCF, BAF ≥ 5000) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000). Vinyl acetate is not expected to bioconcentrate in terrestrial or aquatic organisms, nor to bio-magnify in food chains.

Table 6: Modelled data for bioaccumulation

Test Organism	Endpoint	Value wet wt	Reference
Fish	BAF	1.12 L/kg	Modified GOBAS BAF T2MTL Arnot and Gobas 2003
Fish	BCF	3.28 L/kg	OASIS BCF max, OASIS Forecast v. 1.20, 2005
Fish	BCF	1.65L/kg	BCFWIN v2.15, 2000

Potential to Cause Ecological Harm

Experimental data suggests that no significant harm to aquatic organisms occurs at low concentrations. Ecotoxicity values range from 14 mg/L for fathead minnow (Pickering and Henderson 1964, 1966) to 330 mg/L for daphnia (ECOTOX 2007). Results obtained using a conservative generic exposure scenario (using the model SCREEN3 v.96043, 1995) were compared to long term inhalation toxicity data (stated in Appendix IV) and showed that exposure resulting in ecological harm is not expected. Vinyl acetate is unlikely to cause ecological harm in Canada.

Potential to Cause Harm to Human Health

Exposure Assessment

Upper-Bounding Estimates of Intake From Environmental Media.

It was estimated that the upper-bounding estimate of intake from ambient air, indoor air, solid, drinking water, and food and beverages in Canada to vinyl acetate monomer was 1.76 ug/kg-bw/day. This however, is conservative based on a limit of detection of 10 ug/kg applied to nine food commodity types where vinyl acetate monomer was not detected in any samples in a U.K. food migration study (UK Food Standards Agency, 2004; Health Canada, 2008c). When null values are applied to the nine food commodities, the upper-bounding of intake from environmental media drops to 0.73 ug/kg-bw/day and the greatest source of environmental exposure becomes indoor air as opposed to food sources (Appendix I).

This is substantiated from analysis of food packaging indicating levels of residual vinyl acetate monomer below limits of detection(LOD) < 25 ppm. This was validated via third party lab analyses (Celanese Int. Corp. 2008).

In this regard, the highest mean ambient air concentration of 4.7 ug/m^3 recorded across 20 locations in the U.S. was identified. In contrast, in an air monitoring study conducted in Chicago (U.S. EPA, 2006a), a significantly lower indoor air concentration of 0.7 ug/m^3 was obtained from four locations during August 2001 and March 2002 (Hodgson 2004). The indoor values are considered to be representative of exposure because Canadians spend 3 hours outdoors and 21 hours indoor each day (Health Canada 1998).

Upper-Bounding Estimates of Intake from Consumer Products

Based on input resulting from public consultation and input from industry, new analytical data on consumer products available in the North American marketplace was received (Celanese Int. Corp. 2008). This was in response to information received by Health Canada under the s71 survey which was not suitable for carrying out a consumer exposure assessment. For all consumer product categories tested, all mean and 90th percentile values of residual vinyl acetate (rVA) were below 300 ppm. The highest residue levels identified were for the glues and adhesives category. Other product categories included caulks, spackling, joint compounds, paints, paper goods and food packaging. For instances where no residual

monomer was detected, the residue for the product was assumed to be below the limit of detection of the instrumentation.

Subsequent consumer exposure modelling in RIVM's ConsExpov. 4.1 software (RIVM, 2007) of the Netherlands was performed on highest 90th percentiles of detected residual vinyl acetate monomer or the lowest limit of detection(LOD) for analyses where VAM residues were below the LOD (Table 7 and Appendices II). For some products that were subject to analysis no exposure product scenarios were available. For modelling purposes, based on consideration of the absorption uptakes of the PBPK model as reported in the draft EU RAR, 2008 and the limitations and uncertainty in the scientific database supporting the PBPK model, 100% uptake by the oral, and dermal routes was used and 50% uptake by the inhalation route for ConsExpo v. 4.1 modelling purposes (note the PBPK modelling projected dermal uptake of 90%). These conservative uptakes would result in slightly higher modelled exposures compared to those that may be occurring.

Table 7. ConsExpo v. 4.1 models (see Appendix II)

Modelled consumer product at specified residue level	**Dermal acute(internal dose) mg/kg**	**Dermal chronic (internal dose) mg/kg/day**	**Inhalation mean event concentration mg/m3**	**Inhalation chronic (internal dose) mg/kg/day**	**Oral acute (internal dose) mg/kg**	**Oral chronic (internal dose) mg/kg/day**
Wood glue at 90th percentile 300 ppm	3.39×10^{-4}	4.84×10^{-5}	1.15×10^{-1}	3.13×10^{-4}	-	-
Hot-melt adhesive at 20 ppm (from product intended for consumer use)	2.82×10^{-5}	9.27×10^{-7}	5.75×10^{-2}	3.75×10^{-6}	-	-
Carpet adhesive at lowest LOD of 5 ppm	1.59×10^{-5}	1.0×10^{-8}	5.4×10^{-2}	2.2×10^{-7}	-	-
Food packaging	-	-	-	-		
Latex paint based on 90th percentile 5.2 ppm residual	2.64×10^{-4}	7.23×10^{-7}	0.102 mg/m^3	2.93×10^{-6}	-	-
Plaster (large hole filler) at 0.5 ppm	3.1×10^{-10}	8.5×10^{-13}	-	-	-	-
Plaster (large hole filler not powder form) at 0.5 ppm	3.53×10^{-6}	9.65×10^{-9}	-	-	-	-
Plaster one wall	4.23 x 10-5	2.32 x 10-8	-	-	-	-
Spackling/ jointing compound at 20 ppm 90th percentile	1.41×10^{-5}	1.16×10^{-7}	2.59×10^{-2}	4.05×10^{-6}	-	-

Modelled consumer product at specified residue level	Dermal acute(internal dose) mg/kg	Dermal chronic (internal dose) mg/kg/day	Inhalation mean event concentration mg/m3	Inhalation chronic (internal dose) mg/kg/day	Oral acute (internal dose) mg/kg	Oral chronic (internal dose) mg/kg/day
Teether at 10 ppm[1] 0-5 months age	-	-	-	-	2.05×10^{-4}	2.04×10^{-4}
Hair care at 90th percentile of 30 ppm	2.12×10^{-4}	2.12×10^{-4}	4.84×10^{-4}	5.53×10^{-5}	-	-
Nail polish	-	-	2.4×10^{-1}	4.1×10^{-5}	-	-
Mascara	-	-	3.5×10^{-3}	2.6×10^{-4}	-	-
Eye liner	7.0×10^{-5}	7.0×10^{-5}	2.33×10^{-5}	1.77×10^{-6}	-	-
Caulk at 90th percentile of 25 ppm	5.29×10^{-4} mg/kg	4.34×10^{-6}	1.5×10^{-1}	4.5×10^{-6}	-	-
Wood filler (putty tube) at lowest LOD of 5 ppm	3.53×10^{-7}	2.9×10^{-9}	3.75×10^{-4}	5.86×10^{-8}	-	-
Personal wipes at 90th percentile of 24 ppm	6.77×10^{-6}	6.77×10^{-6}	-	-	-	-

WPEM model results: Comparison with ConsExpo v4.1 estimation of exposure from consumer do-it-yourself painting

The results from the US EPA's Wall Paint Exposure Model (WPEM, US EPA 2001) for a "do-it-yourself" painter, were comparable in magnitude to those estimated by ConsExpo v.4.1 (see Appendix II, III). For instance, the chronic (internal) dose estimated by ConsExpo v.4.1 was 2.93×10^{-6} mg/kg/day whereas the lifetime average daily doses for WPEM scenarios 1 and 2 were 4.35×10^{-7} and 4.02×10^{-6} mg/kg/day. Also, comparatively, the ConsExpo v.4.1 mean event concentration on the day of exposure was 9.4×10^{-3} mg/m^3 whereas, the highest 8-hour average concentrations to which an individual would be exposed from the two WPEM scenarios were lower, 7.86×10^{-4} mg/m^3 and 1.92×10^{-3} mg/m^3 respectively. Thus the ConsExpo values are considered in the overall exposure estimation.

Adhesives- Carpet adhesives

The highest monitored air emission during the gluing of a carpet with adhesive containing vinyl acetate was 2.6 mg/m^3 (Hoescht, 1993 as cited in draft EU RAR 2008). However based on information received, this adhesive is not currently used in the Canadian consumer marketplace.

As part of the industry consultation with Health Canada following the release of the draft vinyl acetate screening assessment, it was communicated that use of styrene-butadiene rubber (SBR) adhesives are predominant in the North American marketplace (Celanese Int. Corp. 2008).

[1] Note that of 8 samples, 7 were below the limit of detection (10 ppm) and one was 13 ppm

In the original studies, Hodgson et al. 1992a,b and 1993, the analyses performed at the University of California, Berkeley, California, concluded that the source of vinyl acetate emissions was from the PVC secondary backing. Of note, the backing adhesive was unspecified. In this study, four different carpet samples were tested in a 20 m^3 environmental test chamber over a period of one week. After 3 hours, initial concentration was 1 mg/m^3 while after 168 hours, it lowered to 0.036 mg/m^3

Because of changes brought about by concern related to indoor release of volatiles, the vinyl acetate industry was asked to characterize changes in carpet industry design in North America. They reported that reduced vinyl acetate emissions have been targeted (Celanese Int. Corp. 2008). It was also reported that vinyl acetate monomer has been used in the manufacture of carpet tiles for many years. Today, two types of precoats are being used in the existing marketplace namely, vinyl acetate ethylene (VAE) copolymer used in conjunction with PVC main backings and the second; ethylene vinyl acetate (EVA) used primarily in conjunction with olefin based main backings.

To address indoor emissions, in the early 1990s, a new voluntary program was introduced to lower carpet contribution to VOC emissions (Celanese Int. Corp. 2008). Consequently, the Carpet and Rug Institute developed the Green Label standard restricting total VOCs to 500 $ug/m^2/hr$ at 24 hrs as measured using ASTM D5116-97 Standard Guide for Small-Scale Environmental Chamber Determinations of Organic Emissions from Indoor Materials/ Products. This has since been modified to a Green Label Plus with a threshold limit of 400 $ug/m^2/hr$. Additional test results from EVA precoated carpet tiles, the predominant product, were submitted demonstrating that there are no detectable levels of (residual vinyl acetate) rVA when contemporary carpets are tested using contemporary methods with an LOD of 10 ppm. Using these data, assuming chamber studies at 24 hrs and a chamber volume of 0.1 m x 0.1m x 0.1 m, the maximum area of carpet in the chamber that was possible was 0.1 m x 0.1 m or 0.01 m^2 carpet. With the BQL (Below Quantifiable Limit) of 0.01 $ug/m^2/hr$, the maximum air chamber concentration possible is BQL x 0.01 m^2 carpet x 24 hrs / 0.1 m^3 chamber volume (rounded up) or 2.4 ug/m^3 which agrees well with the 2.5 ug/m^3 LOD value supplied by industry as evidence. To extrapolate the BQL of 0.01 $ug/m^2/hr$ to an indoor air concentration in a room volume equivalent to that of the 20 m^3 chamber study of Hodgson et al. (1992a,b, 1993) with a similar initial duration of 3 hours, a value of 1.2 x 10^{-5} mg/m^3 is derived vs. the initial 3 hr concentration of 1 mg/m^3 as reported by the EU RAR and Hodgson et al.1992 a, b, 1993, clearly indicating consumer exposure from modern carpets is lower than that estimated from carpets used in the Hodgson studies.

Food packaging adhesives and Food packaging

Adhesives applied to food packaging, cover seams and surfaces thus, rarely are in direct contact with foods. In Canada, vinyl acetate is not classified as a food additive (Division 16 of the Food and Drugs Regulations) (Justice Canada, 2008). A number of food packaging articles were tested for rVA along with the seam area of some e.g. grocery bags. Upon third party validation, the rVA was < 10 ppm for food packaging articles such as fast food packaging and grocery articles. The 90th percentile of rVA from film food wraps was 10 ppm (Celanese Int. Corp. 2008)

Paints and plasters

Zeh et al. (1994) reported calculated and experimental VOC concentrations for the sum of Vinyl acetate and acetaldehyde in indoor air of two offices (I and II), during and after the application of emulsion paints and plasters. Maximum experimental office VOC concentrations of both vinyl acetate and acetaldehyde were 27 mg/m^3 and 13 mg/m^3, respectively for paints formulated with the technology available at that time.

Zeh (2000) analysed spiked paints with vinyl acetate. The 2000 and 1994 studies had comparable findings correlating well between experimental and Zeh's modelled data. Paint spiked prior to application at 1200 ppm vinyl acetate resulted in air room levels of 10 mg/m^3. An extrapolation of these findings to current paints having levels of residual VAM < 10 ppm yields an indoor air concentration of vinyl acetate post-application of < 0.1 mg/m^3 (EU RAR, 2008).

Further information supporting the view of low levels of vinyl acetate originating from consumer painting includes a study by Kominsky and Freyberg (1992) who examined exposures of VOC components of PVA emulsion paints during application and drying. (The target concentration of vinyl acetate in the PVA emulsion upon manufacturing was 3000 ppm.) The content of residual monomer in the samples of paint used in the study was < 1 to 8.2 ppm. Vinyl acetate residues were not detected in either the samples of the personal breathing zone of the applicators or those from the fixed sampling stations in the room. The average environmental LOD with respect to fixed-station area air samples (measurements during application and drying, up to 6 hrs after application) was 0.01ppm = 36 ug/m^3. The average environmental LOD for personal breathing zone concentrations during paint application was 0.22 ppm (Kominsky and Freyberg 1992 in EU RAR 2008). Average environmental detection limits varied from 0.01 to 0.37 ppm (35.2-1302 ug/m^3) for all sampling phases and application methods. An explanation for the low levels of residual vinyl acetate is that typical water-based latex paints are alkaline (pH 8-9) and any residual vinyl acetate in these paints is rapidly hydrolysed under alkaline conditions to acetic acid and acetaldehyde (k_{hydro}= 1.61 mol/s). In comparison, acidified dispersion paints hydrolyse residual vinyl acetate (k= 0.0021 mol/s) much slower (EU RAR 2008). The above reduction in residues observed by Kominsky and Freyberg is explained by this hydrolysis. From this perspective, vinyl acetate emissions from paints are low.

Tobacco products

Filtered cigarettes, because of the use of cellulose prefilters, are a potential source of exposure to vinyl acetate through secondary exposure of bystanders and directly to consumers. It has been reported that cigarettes with cellulose filters release from 200 to 400 ng vinyl acetate /cigarette (Diekmann et al 2002, ATSDR, 1992).

As vinyl acetate monomer is a very minor component of the many constituents of tobacco smoke and its associated products, its potential for exposure is dependent on individual smoking habits and contribution to exposures are considered limited. During the internal consultation phase, no data was received from Health Canada's Tobacco Control Programme.

Other analyses

Various other submissions of confidential information regarding residues of vinyl acetate in consumer products was received to address data quality issues surrounding section 71 solicited data. These data provided additional corroboration of the analytical levels of residual vinyl acetate in consumer products. This supports qualitatively the weight of evidence of analytical levels that currently exists of residual vinyl acetate monomer in consumer products.

Health Effects Assessment

In 1995, the International Agency for Research on Cancer (IARC) concluded that vinyl acetate is "possibly carcinogenic to humans (Group 2B)" on the basis of "inadequate evidence" in humans for the carcinogenicity of vinyl acetate and "limited evidence" of carcinogenicity in experimental animals (IARC 1995). This classification was based on three lines of evidence existing at that time: "(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 1987). 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 specific vinyl acetate animal carcinogenicity and genotoxicity data presented in IARC (1995) are summarized here and in greater detail in Appendix IV. Male and female rats were exposed to vinyl acetate by inhalation at concentrations from 50, 200, and 600 ppm (equivalent to 176, 704, and 2112 mg/m^3) for 104 weeks (Bogdanffy et al. 1994a). A significantly increased incidence ($p<0.01$) of nasal cavity tumours were observed in both sexes of the 600 ppm group. In the same study, groups of mice exposed for 104 weeks to vinyl acetate by inhalation (50 to 600 ppm, equivalent to 176 to 2112 mg/m^3) did not display any exposure-related tumours (Bogdanffy et al. 1994a). In an oral drinking water study, male and female rats that were exposed *in utero*, during lactation, and then for 104 weeks to vinyl acetate in the drinking water (200 to 5000 ppm, equivalent to 10 to 320 mg/kg-bw/day) did not show any exposure-related increases in tumour incidence (Bogdanffy et al. 1994b).

Mixed genotoxicity results for vinyl acetate are shown in Appendix IV. IARC (1995) concluded that vinyl acetate is genotoxic in human cells *in vitro* and animal cells *in vivo*. Vinyl acetate was negative for gene mutations *in vitro* in *S. typhimurium* or SOS repair functions in *E. coli*. (Lijinksky and Andrews 1980; McCann et al. 1975; Brams et al. 1987; Florin et al. 1980; Bartsch et al. 1979). Vinyl acetate was genotoxic in a number of *in vitro* assays including sister chromatid exchange in mammalian and non-mammalian cells, chromosomal aberrations and micronucleus induction, DNA cross-links and cell transformation in mammalian cells (Norppa et al. 1985; He and Lambert 1985; Sipi et al. 1992; Jantunen et al. 1986; Maki-Paakanen and Norppa 1987; Kuykendall and Bogdanffy 1992; Kuykendall et al. 1993; Lambert et al. 1985; Casto 1981). Positive results were observed *in vitro* in *E.coli* in the presence of activation for DNA protein cross-links (Kuykendall & Bogdanffy 1992). Positive results were observed *in vivo* in mice including micronucleus induction, sister chromatid exchange (Maki-Paakanen and Norppa 1987; Takeshita et al. 1986). However, negative results were obtained *in vivo* for the formation of DNA adducts in rats and meiotic micronucleus induction in mice (Lahdetie 1988; Simon et al. 1985). Mixed results for other genotoxicity studies were also reported by ATSDR (1992), NTP (1999), and BUA (1994) (see Appendix IV). The lack of consistency across the different assays do not support a very strong weight of evidence for genotoxicity, but does indicate caution in the assessment.

More recent data on the carcinogenicity of vinyl acetate are summarized here and presented in more detail in Appendix IV. In a study in both mice and rats, exposure to vinyl acetate in the drinking water (400 to 10000 ppm, equivalent to 42 to 1418 mg/kg-bw/day in mice and 21 to 575 mg/kg-bw/day in rats) for 104 weeks resulted in an increase in the incidence of squamous cell tumours in the upper gastro-intestinal tract (GIT) in both sexes of mice and rats (Umeda et al. 2004). The carcinogenic effects of vinyl acetate were also investigated in three other drinking water studies of varying quality (concentrations of 1000 and 5000 ppm) conducted by the same laboratory: in mice (Maltoni et al. 1997), and in two strains of rat (Minardi et al. 2002; Belpoggi et al. 2002). All three studies reported an increased incidence of squamous cell carcinomas in tissues of the upper GIT (oral cavity, esophagus, forestomach) of both sexes of mice and rats. Although some limitations have been reported for these studies, similar target tissues and lesion types were observed following oral exposure to vinyl acetate in drinking water. Taken together these data support the IARC (1995) evaluation on the carcinogenicity of vinyl acetate (IARC 1995).

The de novo development and analysis of the mode of action of a chemical is beyond the scope of a screening assessment, however the European Union has developed and reviewed such a mode of action. Based on the application by the EU of the IPCS conceptual framework for evaluating a mode of action for chemical carcinogenesis (Sonich-Mullin et al 2001) which incorporates data from the peer reviewed literature and manufacturers, and subsequent analysis by the EU rapporteur and member states, the report proposes the existence of a threshold for vinyl acetate carcinogenicity in vivo (EU RAR 2008).

The EU RAR (2008) document also examined the overall carcinogenic potential by the inhalation and oral routes of administration and confirmed that vinyl acetate produced treatment related tumours at the initial sites of contact along these exposure routes, an observation that HC concurs with. The report further demonstrates, using experimental data, that exposure to vinyl acetate results in its metabolism yielding acetic acid and acetaldehyde within the intracellular milieu, and proposes that only when a threshold is surpassed, overwhelming cellular homeostasis and DNA repair mechanisms, does carcinogenicity become evident in the animal studies.

The mode of action elaborated in the EU RAR (2008), and also in the peer reviewed scientific literature, proposes for the olfactory epithelium an initial cytotoxic event (from intracellular acidification from the build up of acetic acid), followed by cell proliferation in response to the resulting cytoxic injury and concurrent genotoxicity (DNA-Protein crosslinking mediated by acetaldehyde) which results in tumours.

Vinyl acetate can therefore be considered a chemical which must achieve a large enough concentration to surmount this threshold, thus overwhelming cellular homeostatic mechanisms and creating the conditions required for the nasal tumours.

For the other tumour sites, the non-olfactory epithelium as well as upper gastrointestinal tract (GIT) mucosa, a similar concentration-dependent increase cell proliferation coupled with the genotoxic action of acetaldehyde, at high concentrations of acetaldehyde, were considered in the EU RAR (2008) to result in tumour development, however it was concluded that the cellular cytotoxicity, as seen in the olfactory epithelium, was not likely a key event in the GIT tumour response (EU RAR, 2008, Kuykendall et al, 1993).

It is consistent with the current state of information on the localization of carboxylesterase, that following oral dosing vinyl acetate is metabolized to produce acetaldehyde by local enzymes along buccal cavity and the GIT (Simon et al. 2002, Morris et al. 2002) and with high doses of vinyl acetate this results in the tumours seen (Appendix IV) .

In humans, acetaldehyde has been identified as an endogenous metabolite, with concentrations exhaled ranging from 0.2 – 0.6 nm/l (Jones, 1995) . Normally acetaldehyde is detoxified by metabolism by acetaldehyde dehydrogenase. In the circumstances of alcohol consumption, significant increases in breath acetaldehyde levels can be achieved ranging from 10-20 nm/l and 20-40nm/l in blood, at blood ethanol concentrations of 10 and 20 umol/l, respectively. This would correspond to corresponding pulmonary blood acetaldehyde concentrations of 2-4 and 4-8 nm/l, respectively (Eriksson, 2007). In comparison populations who inherit an inactive form of below KM mitochondrial isoenzyme of aldehyde dehydrogenase have acetaldehyde levels of 200-500 nm/l at peak following alcohol consumption (Jones, 1995).

Evidence of the role of acetaldehyde, generated endogenously from an exogenous chemical, in upper aerodigestive tract cancer is derived from genetic linkage studies in alcoholics. Polymorphism or mutation in genes encoding for acetaldehyde generation or detoxification are associated with enhanced cancer risk. It has been shown that individuals carrying the acetaldehyde dehyderogenase 2*2 (AALDH 2*2) allele have a significantly increased aerodigestive tract cancer risk when they consume alcohol (Seitz and Meier, 2007).

To illustrate the existence of dose-dependent transition in mechanisms of toxicity the International Life Sciences Institutes (ILSI) and Environmental Sciences Institute (HESI) constituted a working group to develop various case studies to document the existence of a practical thresholds for some carcinogens. Among those discussed, vinyl acetate was presented as a compound demonstrating an inhalation threshold (Slikker et al. 2004).

Regarding the genotoxicity potential of vinyl acetate, the EU RAR report (2008) stated that the genotoxicity data on vinyl acetate metabolites are in line with the hypothesis that vinyl acetate genotoxicity is mediated by acetaldehyde. Having examined the EU RAR and the published literature, Health Canada concurs with this interpretation, and furthermore concludes that the genotoxicity of acetaldehyde only becomes evident after the cellular defence mechanisms are overloaded. Therefore genotoxic consequences, at those sites directly impinged by vinyl acetate (site of first contact) cannot be completed excluded, because the occurrence and strength of the toxicological effects will be totally dependent on the vinyl acetate exposure levels and endogenous metabolic capacity (carboxylesterase and acetaldehyde dehydrogenase) of those tissues directly exposed (e.g. nasal).

Therefore, considering the available evidence, the human relevance of the animal MOA for vinyl acetate effects following inhalation exposure cannot be reasonably excluded on the basis of any identified fundamental, qualitative differences in key events between experimental animals and humans. Furthermore, it appears that vinyl acetate does not cause a carcinogenic response at places distal/remote to the portal of entry; i.e. it is not a systemic carcinogen.

On this basis, a practical threshold for vinyl acetate via the inhalation route of exposure is supported. Specifically, *in vivo* metabolism of vinyl acetate to acetaldehyde and acetic acid, at the point of entry (nasal), will not result in intracellular acidification provided the levels are less than

this threshold and thus is protective against adverse nasal effects. Similarly, although oral exposure to vinyl acetate to the general population is considered negligible, a defensible mode of action for carcinogenicity involving a threshold for induction of effects has been developed for this route (EU RAR 2008). Potential for variability in biological response due to, for example polymorphism in detoxification, DNA repair mechanisms, is acknowledged.

Internationally, the European Union, Technical Committee for Classification and Labelling stated that it used a threshold mode of action for vinyl acetate, when a carcinogenicity Category 3 classification[2], Risk Phrase 40 (limited evidence of carcinogenic effect), in addition to Risk Phrase 20 (harmful by inhalation) and Risk Phrase 37 (irritating to the respiratory system) were proposed to revise the EU classification (EU C&L 2007).

The following sections report the health effects and associated lowest-observed-(adverse)-effect concentrations/levels (LO(A)ECs/LO(A)ELs) that are considered most critical for the purposes of this screening assessment. More detail on the health effects data considered in the assessment can be found tabulated in Appendix IV.

For the health effects from inhalation exposure, the lowest LO(A)ECs for acute, short-term and longer-term exposures are considered separately. For acute inhalation, a range of acute inhalation lowest LO(A)ECs from 4 to 34 ppm (equivalent to 14 to 120 mg/m$^{3)}$ was identified based on a controlled human exposure study (Smyth & Carpenter 1973). These acute inhalation LO(A)ECs are based on reports from the study authors of minimal irritation of the eyes, nose and throat in one of nine volunteers at a concentration as low as 4 ppm following a two-minute exposure while persistent throat irritation was reported in one of three volunteers exposed to 34 ppm for two hours (Smyth & Carpenter 1973). From this study, the US EPA proposed 20 ppm (LO(A)EC of 34 ppm) to represent a "no-effect level for notable discomfort" as the point of departure for derivation of an interim Acute Exposure Guideline Level -1 (AEGL-1) (US EPA 2006b). The overall range of acute inhalation LO(A)ECs of 4 to 34 ppm (equivalent to 14 to 120 mg/m^3) is supported by another study in humans (Deese & Joyner 1969) which reports similar irritant effects within the same range of exposure concentrations to vinyl acetate.

From studies of short-term inhalation exposure to vinyl acetate, a range of lowest LO(A)ECs from 528 to 2110 mg/m^3 (150 to 600 ppm) has been identified from among the studies considered in Appendix IV. For the lower end of this range, a LO(A)EC of 528 mg/m^3 (150 ppm) was identified from a 4 week study in mice based on a reported treatment related incidence and severity of respiratory distress and hunched posture (Owen 1979a). Similar effects of respiratory distress and hunched posture were reported by the same author in a following a 4 week exposure in rats (Owen 1979b) and in both mice and rats in longer term studies (90 days in mice & rats, Owen 1980a,b) while exposure in mice and rats in a 2 year study also indicated effects such as rough haircoat and hunched posture (Owen 1988; Bogdanffy et al. 1994a) The Acute Exposure Guideline Level (AEGL) (US EPA 2006b), EU RAR (2008) and the ATSDR (1992) also referred to the hunched posture and respiratory distress reported by Owen 1979a,b. For these studies, the EU RAR (2008) identified a lowest LO(A)EC of 150 ppm based on local effects on the respiratory track in mice. It should be noted that the respiratory distress and hunched posture were reported qualitatively in

[2] Substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment. There is some evidence from appropriate animal studies, but this is insufficient to place the substance in category 2.

Owen (1979a,b) while incidence data available from the 2 year study showed a general lack of dose-dependency for these effects (incidence data cited in Owen 1988). In regards to the hunched posture, the EU RAR stated that it was uncertain whether hunched posture could be interpreted as a non-specific toxic effect and more likely seemed to be associated with the respiratory symptoms. (EU RAR 2008). Despite these limitations, the level of 528 mg/m^3 (150 ppm) from the 4-week mouse study will be considered as a conservative lower limit in the range of lowest inhalation LO(A)ECs. For the upper end of the range of short-term inhalation LO(A)ECs, an effect level of 2110 mg/m^3 was selected based on histopathologic changes and increased cell proliferation in the nasal mucosa of male rats following inhalation exposure to 600 ppm (equivalent to 2110 mg/m^3) for 1, 5, or 20 days (Bogdanffy et al., 1997). The EU RAR (2008) has reported 200 ppm as a NO(A)EC for this study.

From studies of longer-term inhalation exposure to vinyl acetate, a LO(A)EC of 704 mg/m^3 (200 ppm) was identified based on effects both from a 90 day study in mice (Owen 1980a) and also from a 2 year studying mice & rats (Owen 1988; Bogdanffy et al. 1994a). In a study conducted by Owen (1980a), effects were reported in the nasal cavity (diffuse rhinitis, US EPA 1990; inflamation of nasal turbinate, ATSDR 1992) and in the respiratory tract (focal pneumonitis, US EPA (1990); multi-focal bronchitis, ATSDR 1992) of mice at ≥200 ppm (704 mg/m^3). The 200 ppm effect level reported in Owen (1980a) was identified as a LOAEC by the US EPA (1990) and ATSDR (1992). Based on these effects, the NO(A)EC of 50 ppm was also used by the ATSDR for the derivation of an intermediate inhalation minimal risk value (MRL) (ATSDR 1992). The EU RAR also considered 200 ppm of this study as a LO(A)EC based on hunched posture and respiratory distress (EU RAR 2008). In a 2 year chronic study, histopathologic changes of the nasal cavity (atrophy of olfactory epithelium, hyperplasia of basal cells in rats and submucosal cells in mice) and upper respiratory tract (epithelial hyperplasia in the trachei of mice) were also observed at ≥200 ppm (704 mg/m^3) in both mice and rats and this level was considered as a LO(A)EC while 50 ppm (176 mg/m^3) was considered the NO(A)EC by the authors (Bogdanffy et al. 1994a, Owen 1988). The no effect level of 50 ppm from this study was used by the US EPA (1990) for the derivation of a chronic inhalation reference concentration (RFC) and by the EU RAR (2008) for the calculation of chronic inhalation margins of safety. Regarding carcinogenic effects of vinyl acetate, the EU RAR (2008) considered the tumourigenic LO(A)EC from Bogdanffy et al. (1994a) to be 200 ppm (NO(A)EC of 50 ppm) based on the observation of an olfactory papilloma in one male rat at 200 ppm with statistically significant increased nasal tumours at 600 ppm. For the neoplastic effects of vinyl acetate by the inhalation route of exposure, the proposed mode of action (MOA) described in the EU RAR (2008) is being considered in this assessment. Therefore a NO(A)EC value of 50 ppm (176 mg/m^3) from Bogdanffy et al. (1994a) is considered to be the threshold level for neoplastic effects as reported in the EU RAR (2008). IARC (1995) also reported a long term (10 months) inhalation rat study conducted by Czajkowska et al. (1986). Various effects such as body weight changes, reticulopenia, metaplasia of the bronchi and liver toxicity have been reported from concentrations of 10 to 500 mg/m^3, however several limitations were identified for this study. Furthermore, an assessment by SCOEL (2005) considered this study to be less well documented and did not further consider it. In addition, this study was not reported in the most recent assessments (EU RAR 2008, US EPA 2006b). For these reasons, this study was no longer considered in this screening assessment.

For the health effects from oral exposure, a range of oral LO(A)ELs from 31 to 202 mg/kg-bw/day has been identified among the oral drinking water studies considered in Appendix IV. The effect level for the lower limit of this range of LO(A)ELs was identified from a chronic drinking water

study in rats (Umeda et al. 2004) in which a dose-dependent increase in squamous cell carcinomas of the oral cavity of females were reported at ≥ 400 ppm (31 mg/kg-bw/day). The EU RAR (2008) considered the tumourigenic LO(A)EL to be 400 ppm for this study. In addition, it was noted that a clear threshold for carcinogenicity was not established in the study conducted by Umeda et al. (2004) since 400 ppm was the lowest tested dose. Squamous cell carcinomas of the upper GIT were also reported in both sexes of mice and rats at higher concentrations in several drinking water studies (Umeda et al. 2004, Minardi et al. 2002, Belpoggi et al. 2002, Maltoni et al. 1997, Bogdanffy et al. 1994b). For the upper limit of the range of oral LO(A)ELs selected, an effect level of 202 mg/kg-bw/day has been identified from two different chronic drinking water studies in mice and rats (Umeda et al. 2004 & Bogdanffy et al. 1994b respectively). One of the studies reported a dose-dependent increased incidence of hyperplastic changes in the oral cavity in male and female mice at ≥ 2000 ppm (the authors' dose conversion for males of 202 mg/kg-bw/day based on water intake) while statistically significant squamous cell tumours were also observed in both sexes at the next higher dose of 10000 ppm (Umeda et al. 2004). Another long-term drinking water study in rats also reported a LO(A)EL of 202 mg/kg-bw/day based on reduced body weight in males at a concentration of 5000 ppm vinyl acetate (dose conversion from study authors equal to 202 mg/kg-bw/day based on water intake) though decreased water intake and food consumption was also reported at 5000 ppm in this study (Bogdanffy et al. 1994b). The EU RAR considered 202 mg/kg-bw/day to be the LO(A)EL for both of these studies (EU RAR 2008). Overall, the range of lowest oral LO(A)ELs of 31 to 202 mg/kg-bw/day are considered to represent the lower range of effects identified from the available oral studies considered in Appendix IV. However, it should be noted that a non-tumourigenic level was not clearly established at the lower range LO(A)EL concentration since tumours in the oral cavity of female rats were observed at the lower LO(A)EL of 31 mg/kg-bw/day (400 ppm) (Umeda et al. 2004).

Regarding health effects from dermal exposure, no repeated-dose studies were identified in the literature. However, the range of dermal LD_{50} values for rabbits were reported to be from 2330 to 7440 mg/kg-bw (converted from 2.5 – 8 ml/kg-bw, ATSDR 1992). In addition, following an acute dermal study in rabbits, gross lesions were reported in various tissues including: congestion of the lungs and liver, mottled spleen and kidney, and prominent liver acini (Weil and Carpenter 1969, as cited in ATSDR 1992).

Characterization of Risk to Human Health

Based principally on the weight of evidence evaluation of IARC (1995) and taking into consideration more recent data including the EU RAR (2008), the most critical effects in the vinyl acetate experimental database for characterization of risk to human health are reported from inhalation studies. Vinyl acetate induced tumours of the nasal cavity in male and female rats following inhalation exposure while oral exposure to considerably higher levels administered in drinking water were associated, at the highest dose tested, with upper gastro-intestinal tract squamous cell carcinomas in both sexes of two species. Vinyl acetate was also found to be moderately genotoxic (clastogenic) in human cells *in vitro* and in animals *in vivo*.

Although the de novo development and analysis of the mode of action of a chemical is beyond the scope of a screening level assessment, the European Union has developed and critically reviewed such a mode of action using the IPCS conceptual framework for evaluating a mode of action for chemical carcinogenesis (Sonich-Mullin et al 2001, EU RAR 2008. Health Canada having

considered the body of available information and the EU mode of action analysis cannot reasonably exclude the relevance of the proposed animal MOA to humans.

On this basis, it is considered that vinyl acetate demonstrates a threshold for carcinogenicity in nasal tissues for exposures via the inhalation route. It is considered that exposures to inhalation levels below this practical threshold will not result in biological conditions favouring tumour development. Similarly, although oral exposure to vinyl acetate to the general population is considered negligible, a defensible mode of action for carcinogenicity involving a threshold for induction of effects has been developed for this route (EU, RAR, 2008).

For acute exposure, a range of LO(A)ECs from 4 to 34 ppm (14-120 mg/m^3) (Smyth and Carpenter 1973) were considered for the derivation of an acute margin of exposure (MOE) with the 90^{th} percentile of all the ConsExpo v. 4.1 (RIVM 2006) consumer product modelled inhalation mean event concentrations of 0.15 mg/m^3. The acute MOEs range from approximately 100 to 800. Higher confidence is given to the MOE of 800 since effects at 34 ppm were more pronounced and the duration of exposure was longer. In addition, it should be noted that the range of acute LO(A)ECs are derived from a controlled human exposure study which increases the confidence that these margins are considered to be adequate. For short-term exposure, a range of short-term LO(A)ECs from 528 mg/m^3 (Owen 1979a) to 2110 mg/m^3 (Bogdanffy et al. 1997) compared with a 90^{th} percentile of all the ConsExpo v4.1 consumer end-use product modelled inhalation mean event concentrations of 0.15 mg/m^3 results in MOEs of 3.5×10^3 to 1.4×10^4. With respect to non-neoplastic effects, a comparison of the chronic inhalation LO(A)EC of 704 mg/m^3 (Bogdanffy et al. 1994a) with the upper-bounding estimate of general population indoor air concentration of 0.0007 mg/m^3 (Hodgson 2004), results in an MOE above 1.0×10^6. The chronic inhalation NO(A)EC for this study (176 mg/m^3) would result in a MOE of 2.5×10^5. In summary, the MOEs for inhalation effects and the upper bounding estimate of exposure to the general population and from consumer products via inhalation are considered to be adequate No margins of exposure were derived for the oral or dermal routes of exposure as consumer exposures via these routes are considered to be negligible.

Although variability in the ability to detoxify the putatively active metabolite (i.e. acetaldehyde) across the general population associated with genetic polymorphism is recognized, in light of the large MOE for chronic exposures, this margin is considered to be adequately protective for this potentially sensitive subgroup of the population.

On the basis of these considerations, vinyl acetate does not to meet the criteria, using the critical health endpoints examined, under Paragraph 64(c) of CEPA 1999.

Uncertainties in Evaluation of Risk to Human Health

Confidence in the toxicological database for vinyl acetate is considered to be moderate to high as data is available for acute toxicity, repeated dose (oral and inhalation) toxicity, reproductive and developmental toxicity, genetic toxicity and carcinogenicity in experimental animals for oral and inhalation exposure. The inhalation database is, in addition, supported by a pharmacokinetic inhalation model, which was validated using human exposure data. There are some limitations in the data base in that the animal database for the oral route of exposure is not as robust as that for the

inhalation route, plus there are no toxicokinetic data for either the dermal or oral routes of human exposure.

No Canadian environmental media data were available for derivation of the upper-bounding estimates of exposure and surrogate data was used to calculate exposures. Inhalation route was identified as the primary exposure route for both environmental media and consumer products as one would expect from vinyl acetate's vapour pressure and volatile nature. There is a high degree of confidence in consumer product upper-bounding estimates of exposure based on recent survey data of approximately 150 consumer products in the North American marketplace for analysis of residuals of vinyl acetate monomer. Confidence is increased in the exposure assessment from the finding of indoor air being the largest source of environmental media exposures to vinyl acetate monomer. Confidence in the exposure assessment is further strengthened despite minor uncertainties and limitations from use of indoor air data from portable classrooms and outdoor air values from a water treatment plant, defaults of consumer product modelling and; the underlying assumptions of body weights, breathing rates, intakes and exposure durations (Health Canada, 1998).

Conclusion

On the basis of ecological hazard and reported releases of vinyl acetate, it is proposed that this substance is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity, or that constitute or may constitute a danger to the environment on which life depends.

Based on the available information on its potential to cause harm to human health, it is concluded that vinyl acetate is not currently entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore proposed that vinyl acetate does not meet the definition of "toxic" as set out in section 64 of CEPA 1999. Additionally, vinyl acetate does not meet the criteria for persistence and bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

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APPENDIX I: Upper-Bounding Estimates of Exposure to the General Population of Canada from Environmental Media

Estimated Intake (µg/kg b.w./day) of Vinyl acetate monomer to the General Population of Canada by Age								
Age Group:	0 - 0.5 yr [1,2,3]			0.5 - 4 yr[4]	5 - 11 yr[5]	12 - 19 yr[6]	20 - 59 yr[7]	60 + yr[8]
Route of Exposure	Breast Milk Fed	Formula Fed	Not Formula Fed					
Ambient Air[9]	0.16	0.16	0.16	0.35	0.27	0.16	0.13	0.12
Indoor Air[10]	0.17	0.17	0.17	0.37	0.29	0.16	0.14	0.12
Drinking Water[11]	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Food and Beverages[12]	0.00	0.00	0-1.42	0-0.96	0-0.61	0-0.34	0-0.24	0-0.20
Soil[13]	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Total Intake	0.34	0.34	0.34-1.76	0.72-1.68	0.56-1.17	0.32-0.66	0.27-0.52	0.24-0.44
							Maximum Total Intake	0.72-1.76

1 No reported data for concentration of vinyl acetate in breast milk.

2 Assumed to weigh 7.5 kg, to breathe 2.1 m^3 of air per day, to drink 0.8 L of water per day (formula fed) or 0.3 L/day (not formula fed) and to ingest 30 mg of soil per day (Health Canada, 1998).

3 For exclusively formula-fed infants, intake from water is synonymous with intake from food. No data on concentrations of vinyl acetate in formulae were identified for Canada.

4 Assumed to weigh 15.5 kg, to breathe 9.3 m^3 of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil per day (Health Canada, 1998).

5 Assumed to weigh 31.0 kg, to breathe 14.5 m^3 of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil per day (Health Canada, 1998).

6 Assumed to weigh 59.4 kg, to breathe 15.8 m^3 of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil per day (Health Canada, 1998).

7 Assumed to weigh 70.9 kg, to breathe 16.2 m^3 of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil per day (Health Canada, 1998).

8 Assumed to weigh 72.0 kg, to breathe 14.3 m^3 of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil per day (Health Canada, 1998).

9 No Canadian data were identified. As a surrogate, maximum mean concentration value of 4.7 µg/m^3 of vinyl acetate in ambient (outdoor) air reported by US EPA in 2006 was used to calculate the upper bounding limit of exposure estimate. Air monitoring was conducted in Chicago, US with 20 samples taken (US EPA, 2006a). Canadians are assumed to spend 3 hours outdoors each day (Health Canada, 1998).

10 No Canadian data were identified. A maximum concentration value of 0.7 µg/m^3 of vinyl acetate in indoor air from an air monitoring study of standard relocatable classrooms was used to calculate the upper-bounding limit of exposure estimate. The air study of relocatable classrooms was conducted in US with 4 sampling locations during Aug. 2001-Mar. 2002 (Hodgson, 2004). Canadians are assumed to spend 21 hours indoors each day (Health Canada, 1998).

11 No reported data for the concentration of vinyl acetate in drinking water was identified. ChemCan Version 6.0.0. (2003) modeling was run for the top two NPRI releasers from Alberta. The estimated modeled concentration was 0.0001 ug/L. This had no impact on the upper bounding estimates of daily intake.

12 Estimates of intake from food are based on use of the lowest LOD of 10 ug/kg applied to all nine food commodity groups analyzed for vinyl acetate migrating from food packaging in a migration study performed by the UK. Food categories were dairy products, fats, fruits, vegetables, cereal products, meat and poultry, fish, foods that are primarily sugar, mixed dishes and soups (UK Food Standards Agency, 2004). Daily food consumption by age group is outlined by Health Canada (Health Canada, 1998). Null values were also applied and results depicted in the second intake table.

13 No reported data for the concentration of vinyl acetate in soil was identified. ChemCan Version 6.00 modeling was run for the top two NPRI 2005 releasers from Alberta and was modeled in Northern Alberta. The estimated modeled concentration was 0.0013 ug/kg. This had no impact on the upper bounding estimates of daily intake.

APPENDIX II: Upper-Bounding Estimates of Exposure to Vinyl Acetate from Consumer Products*

*** some default factors were obtained from the Cosmetics Division of the Product Safety Programme of Health Canada 1998, 2008 d, RIVM 2006, 7 (several fact sheets)**

No.	Consumer Product Type	Model Parameters	Estimated Exposure
1	Large hole filler plaster	Molecular weight of 86.1 g/mol Vapour pressure of 89.1 mm Hg KOW 0.7 10Log Exposure frequency 1 x / year (RIVM, 2006,7) Adult body weight 70.9 kg (Health Canada, 1998) Weight fraction of 5.0 x 10^{-7} or 0.5 ppm Dermal exposure from direct dermal contact with product applied to skin at a constant rate. Dermal uptake of 100%	Dermal acute (internal) dose: 3.1 x 10^{-10} mg/kg Dermal chronic (internal) dose: 8.47 x 10^{-13} mg/kg/day
2	Large hole filler (not powder)	Molecular weight of 86.1 g/mol Vapour pressure of 89.1 mm Hg KOW 0.7 10Log Exposure frequency 1 x / year (RIVM, 2006,7) Adult body weight of 70.9 kg (Health Canada, 1998) Weight fraction of 5.0 x 10^{-7} or 0.5 ppm Exposed area of 430 cm^2 (RIVM, 2006,7) Applied amount of 0.5 g (RIVM, 2006,7) Dermal exposure from direct dermal contact with product applied at once to skin via instant application. Dermal uptake of 100 %	Dermal acute (internal) dose: 3.53 x 10^{-6} mg/kg Dermal chronic (internal) dose: 9.65 x 10^{-9} mg/kg/day
3	Wall plaster	Molecular weight of 86.1 g/mol Vapour pressure of 89.1 mm Hg KOW 0.7 10Log Exposure frequency 0.2 x / year (RIVM, 2006,7) Adult body weight of 70.9 kg (Health Canada, 1998) Weight fraction of 5.0 x 10^{-7} or 0.5 ppm Exposed area of 1.9 x 10^{-3} cm^2 (RIVM, 2006,7) Contact rate of 50 mg/min (RIVM, 2006,7) Release duration of 120 min (RIVM, 2006,7) Dermal uptake of 100% Dermal exposure from direct contact, product applied to skin at a constant rate.	Dermal acute (internal) dose: 4.23 x 10^{-5} mg/kg Dermal chronic (internal) dose: 2.32 x 10^{-8} mg/kg/day
4	Spackling / Joint compound	Molecular weight of 86.1 g/mol Vapour pressure of 89.1 mm Hg KOW 0.7 10Log Exposure frequency 3 x / year (RIVM, 2006,7) Adult body weight of 70.9 kg (Health Canada, 1998) Weight fraction compound 2 x 10^{-5} or 20 ppm Exposure duration of 240 min (RIVM, 2006,7) Room volume of 20 m^3 (RIVM 2006,7) Ventilation rate of 0.6x / hr (RIVM, 2006,7) Applied amount of 40 g (RIVM, 2006,7) Release area of 200 cm^2 (RIVM, 2006,7) Application duration of 20 min (RIVM, 2006,7) Mol weight matrix of 3 x 10^3 g/mol (RIVM, 2006,7) Mass transfer rate of 4 x 10^3 m/min (RIVM, 2006,7) Uptake fraction 50 % Inhalation rate of 16.2 m^3/day (RIVM, 2006,7) Inhalation model exposure to vapour by evaporation.	Inhalation mean event concentration of: 2.59 x 10^{-2} mg/m^3 Inhalation chronic (internal) dose of: 4.05 x 10^{-6} mg/kg/day
		Molecular weight of 86.1 g/mol Vapour pressure of 89.1 mm Hg KOW 0.7 10Log Adult body weight of 70.9 kg (Health Canada, 1998) Uptake fraction of 100%	Dermal acute (internal) dose of: 1.41 x 10^{-5} mg/kg Dermal chronic (internal) dose of:

		Weight fraction of 2 x 10^{-5} or 20 ppm Exposed area of 22 cm^2 (RIVM, 2006,7) Applied amount of 0.05 g (RIVM, 2006,7) Dermal model: direct dermal contact with product applied to skin at once to skin via instant application.	1.16 x 10^{-7} mg/kg/day
5	Teether	Molecular weight of 86.1 g/mol Vapour pressure of 89.1 mm Hg KOW 0.7 10Log Exposure frequency of 365 x / year (RIVM, 2006,7) 0-0.5 month year old infant body weight of 7.5 kg (Health Canada, 1998) Weight fraction of compound of 1.0 x 10^{-5} or 10 ppm. Product amount of 20 g (RIVM, 2006,7) Leach rate of 1.4 x 10^{-8} g/cm^2/min. This leaching rate is based on a 12-hour vinyl acetate half-life in EVA materials. Contact area of 10 cm^2 (RIVM, 2006,7) Exposure time of 11 min (RIVM, 2006,7) Oral uptake fraction of 100% Oral exposure to product from migration from a mouthed product.	Oral acute (internal) dose: 2.05 x 10^{-4} mg/kg Oral chronic (internal) dose: 2.04 x 10^{-4} mg/kg/day
6	Hair care product	Molecular weight of 86.1 g/mol Vapour pressure of 89.1 mm Hg KOW 0.7 10Log Exposure frequency of 1 x /day (Health Canada, 2008d) Adult body weight of 70.9 kg (Health Canada, 1998) Weight fraction of 3 x 10^{-5} or 30 ppm (90^{th} percentile) Exposure duration of 1.44 x 10^3 min (Health Canada, 2008 d) Room volume of 20 m^3 (RIVM, 2006,7) Ventilation rate of 0.6 x / hr (RIMV, 2006,7) Applied amount of 5 g (Health Canada, 2008 d) Release duration of 1.44 x 10^3 min (Health Canada, 2008d, RIVM, 2006,7) Uptake fraction of 50% Inhalation rate of 16.2 m^3/day (RIVM, 2006,7) Exposure to vapour at constant rate of release.	Inhalation mean event concentration: 4.84 x 10^{-4} mg/m^3 Inhalation chronic (internal) dose: 5.53 x 10^{-5} mg/kg/day
		Molecular weight of 86.1 g/mol Vapour pressure of 89.1 mm Hg KOW 0.7 10Log Adult body weight of 70.9 kg (Health Canada, 1998) Weight fraction of 3 x 10^{-5} or 30 ppm (90^{th} percentile) Dermal direct contact with product applied at once to skin via instant application. Exposed area of 1.01 x 10^3 cm^2 (RIVM, 2006,7) Applied amount of 0.5 g (RIMV, 2006, 7, Health Canada 2008d) Uptake fraction of 100%	Dermal acute (internal) dose: 2.67 x 10^{-4} mg/kg Dermal chronic (internal) dose: 2.67 x 10^{-4} mg/kg/day
7	Nail polish	Molecular weight of 86.1 g/mol Vapour pressure of 89.1 mm Hg KOW of 0.7 10Log Exposure frequency of 156 x / year (Health Canada, 2008d) Adult body weight of 70.9 kg (Health Canada, 1998) Weight fraction of 0.1 or 100,000 ppm Exposure duration of 5 min (Health Canada, 2008d) Room volume of 20 m^3 (RIVM, 2006,7) Ventilation rate of 0.6 x / hr (RIVM, 2006,7) Applied amount of 0.05 g (RIVM, 2006,7) Release area of 1 cm^2 (Health Canada, 2008 d; RIVM, 2006,7) Application duration of 5 min (Health Canada, 2008d; RIVM, 2006,7) Mol weight matrix of 124 g/mol Mass transfer rate of 4.02 x 10^3 m/min Uptake fraction of 50% Inhalation rate of 16.2 m^3/day (RIVM, 2006,7) Inhalation exposure to vapour via evaporation.	Inhalation mean event concentration: 2.44 x 10^{-1} mg/m^3 Inhalation chronic (internal) dose: 4.13 x 10^{-5} mg/kg/day
8	Mascara	Molecular weight of 86.1 g/mol Vapour pressure of 89.1 mm Hg KOW of 0.7 10Log Adult body weight of 70.9 kg (Health Canada, 1998) Exposure frequency of 1 x /day (Health Canada, 2008d)	Inhalation mean event concentration: 3.5 x 10^{-3} mg/m^3

		Body weight of 70.9 kg (Health Canada, 1998) Weight fraction of 0.03 or 30,000 ppm Exposure duration of 960 min (Health Canada, 2008d) Room volume of 20 m^3 (RIVM, 2006,7) Ventilation rate of 0.6 x /hr (RIVM, 2006,7) Applied amount of 0.025 g (Health Canada, 2008d) Release duration of 960 min (Health Canada 2008d; RIVM, 2006,7) Uptake fraction of 50% Inhalation rate of 16.2 m^3/day (RIVM, 2006,7) Exposure to vapour at a constant rate	Inhalation chronic (internal) dose: 2.7 x 10^{-4} mg/kg/day
9	Eye liner	Molecular weight of 86.1 g/mol Vapour pressure of 89.1 mm Hg KOW of 0.7 10Log Exposure frequency of 1 x /day (Health Canada, 2008d) Adult body weight of 70.9 kg (Health Canada, 1998) Weight fraction of 0.001 or 1,000 ppm Exposure duration of 960 min (Health Canada, 2008d) Room volume of 20 m^3 (RIVM, 2006,7) Ventilation rate of 0.6 x/hr (RIVM, 2006,7) Applied amount of 0.005 g (Health Canada, 2008d) Release duration of 960 min Uptake fraction of 50% Inhalation rate of 16.2 m^3/day (RIVM, 2006,7) Inhalation model: exposure to vapour at a constant rate	Inhalation mean event concentration: 2.33 x 10^{-5} mg/m^3 Inhalation chronic (internal) dose: 1.77 x 10^{-6} mg/kg/day
		Molecular weight of 86.1 g/mol Vapour pressure of 89.1 mm Hg KOW of 0.7 10Log Adult body weight of 70.9 kg (Health Canada, 1998) Weight fraction of 0.001 or 1,000 ppm Exposed area of 3.2 cm^2 (Health Canada, 2008d) Applied amount of 0.005 g (Health Canada, 2008d) Uptake fraction of 100% Direct dermal model, product applied at once to skin via instant application.	Dermal acute (internal) dose: 7.05 x 10^{-5} mg/kg Dermal chronic (internal) dose: 7.23 x 10^{-5} mg/kg/day
10	Caulk	Molecular weight of 86.1 g/mol Vapour pressure of 89.1 mm Hg KOW of 0.7 10Log Caulk exposure frequency of 3 x / year (RIVM, 2006,7) Adult body weight of 70.9 kg (Health Canada, 1998) Weight fraction of 2.5 x 10^{-5} or 25 ppm (90^{th} percentile) Exposure duration of 45 min (RIVM, 2006,7) Room volume of 10 m^3 (RIVM, 2006,7) Ventilation rate of 0.6 x / hr (RIVM, 2006,7) Applied amount of 75 g (RIVM, 2006,7) Release duration of 250 cm^2 (RIVM, 2006,7) Application duration of 30 min (RIVM, 2006, 7) Mol weight matrix of 3 x 10^{-3} g/mol (RIVM, 2006,7) Mass transfer rate of 4 x 10^{-3} m/min (RIVM, 2006,7) Uptake fraction of 50% Inhalation rate of 16.2 m^3/day (RIVM, 2006,7) Inhalation model used was model for evaporation exposure to vapour. Release area is constant over time.	Inhalation mean event concentration of: 1.54 x 10^{-1} mg/m^3 Inhalation chronic (internal) dose of : 4.53 x 10^{-6} mg/kg/day
		Molecular weight of 86.1 g/mol Vapour pressure of 89.1 mm Hg KOW of 0.7 10Log Adult body weight of 70.9 kg (Health Canada, 1998) Weight fraction of 2.5 x 10^{-5} or 25 ppm (90^{th} percentile) Exposed area of 2 cm^2 (RIVM, 2006,7) Contact rate of 50 mg/min Release duration of 30 min Dermal model: direct dermal contact with product at a constant rate.	Dermal acute (internal) dose: 5.29 x 10^{-4} mg/kg Dermal chronic (internal) dose : 4.34 x 10^{-6} mg/kg/day
11	Wood filler (putty tube)	Molecular weight of 86.1 g/mol Vapour pressure of 89.1 mm Hg KOW of 0.7 10Log Exposure frequency of 3 x / year (RIVM, 2006,7)	Inhalation mean event concentration of: 3.75 x 10^{-4} mg/m^3

		Adult body weight of 70.9 kg (Health Canada, 1998) Weight fraction of 5 x 10^{-7} or 0.5 ppm (Lowest LOD) Exposure duration of 240 min (RIVM, 2006,7) Room volume of 20 m^3 (RIVM, 2006, 7) Ventilation rate of 0.6 x / hr (RIVM, 2006,7) Applied amount of 40 g (RIVM, 2006,7) Release area of 200 cm^2 (RIVM, 2006,7) Application duration of 20 min (RIVM, 2006,7) Mol weight matrix of 3 x 10^3 g/mol (RIVM, 2006,7) Mass transfer rate of 4.02 x 10^3 m/min (RIVM, 2006,7) Uptake fraction of 50% Inhalation rate of 16.2 m^3 /day (RIVM, 2006,7) Inhalation model exposure to vapour via evaporation.	Inhalation chronic (internal) dose: 5.86 x 10^{-8} mg/kg/day
		Molecular weight of 86.1 g/mol Vapour pressure of 89.1 mm Hg KOW of 0.7 10Log Adult body weight of 70.9 kg (Health Canada, 1998) Weight fraction of 5 x 10^{-7} or 0.5 ppm (Lowest LOD) Exposed area of 22 cm^2 (RIVM, 2006,7) Applied amount of 0.05 g (RIVM, 2006,7) Uptake fraction of 100% Direct dermal model product applied to skin at a constant rate.	Dermal acute (internal) dose: 3.53 x 10^{-7} mg/kg Dermal chronic (internal) dose: 2.9 x 10^{-9} mg/kg/day
12	Wood glue	Molecular weight of 86.1 g/mol Vapour pressure of 89.1 mm Hg KOW of 0.7 10Log Adult body weight of 70.9 kg (Health Canada, 1998) Exposure frequency of 1 x /week (RIVM, 2006,7) Weight fraction of 0.003 or 300 ppm (90^{th} percentile) Exposure duration of 240 min (RIVM, 2006,7) Room volume of 20 m^3 (RIVM, 2006,7) Ventilation rate of 0.6 x / hr (RIVM, 2006,7) Applied amount of 10 g (RIVM, 2006,7) Release area of 400 cm^2 (RIVM, 2006,7) Application duration of 20 min (RIVM, 2006,7) Mol weight matrix of 3 x 10^3 g/mol Mass transfer rate of 4.0 x 10^3 m/min Uptake fraction of 50% Inhalation rate of 16.2 m^3/day (RIVM, 2006,7) Inhalation model: Exposure to vapour: evaporation	Inhalation mean event concentration: 1.15 x 10^{-1} mg/m^3 Inhalation chronic (internal) dose: 3.13 x 10^{-4} mg/kg/day
		Molecular weight of 86.1 g/mol Vapour pressure of 89.1 mm Hg KOW of 0.7 10Log Adult body weight of 70.9 kg (Health Canada, 1998) Weight fraction of 0.0003 or 300 ppm (90^{th} percentile) Exposed area of 2 cm^2 (RIVM, 2006,7) Applied amount of 0.08 g (RIVM, 2006,7) Uptake fraction of 100% Dermal model: direct dermal contact with product, instant application	Dermal acute (internal) dose: 3.4 x 10^{-4} mg/kg Dermal chronic (internal) dose: 4.84 x 10^{-5} mg/kg/day
13	Hot melt adhesive	Molecular weight of 86.1 g/mol Vapour pressure of 89.1 mm Hg KOW of 0.7 10Log Exposure frequency of 1 x / month (RIVM, 2006,7) Adult body weight of 70.9 kg (Health Canada, 1998) Weight fraction of 2.0 x 10^{-5} or 20 ppm (from product intended for consumer use) Exposure duration of 25 min (RIVM, 2006,7) Room volume 20 m^3 (RIVM, 2006,7) Ventilation rate of 0.6 x / hr (RIVM, 2006,7) Applied amount of 65 g (RIVM, 2006,7) Uptake fraction of 50% Inhalation rate of 16.2 m^3/day (RIVM, 2006,7) Inhalation model: exposure to vapour: instantaneous release.	Inhalation mean event concentration: 5.75 x 10^{-2} mg/m^3 Inhalation chronic (internal) dose: 3.75 x 10^{-6} mg/kg/day
		Molecular weight of 86.1 g/mol Vapour pressure of 89.1 mm Hg KOW of 0.7 10Log	Dermal acute (internal) dose: 1.42 x 10^{-4} mg/kg

		Adult body weight of 70.9 kg (Health Canada, 1998) Weight fraction of 2 x 10^{-5} or 20 ppm (from product intended for consumer use) Exposed area of 43 cm^2 (RIVM, 2006,7) Applied amount of 100 mg (RIVM, 2006,7) Uptake fraction of 100% Dermal model: direct dermal contact with product, instant application.	Dermal chronic (internal) dose: 4.67 x 10^{-6} mg/kg/day
14	Carpet adhesive	Molecular weight of 86.1 g/mol Vapour pressure of 89.1 mm Hg KOW of 0.7 10Log Adult body weight of 70.9 kg (Health Canada, 1998) Exposure frequency of 0.25 x / year (RIVM, 2006,7) Weight fraction of 5 x 10^{-7} or 0.5 ppm Exposure duration of 75 min (RIVM, 2006,7) Room volume of 58 m^3 (RIVM, 2006,7) Ventilation rate of 0.6 x / hr (RIVM, 2006,7) Applied amount of 9 x 10^3 g (RIVM, 2006,7) Release area of 4 m^2 (RIVM, 2006,7) Application duration of 75 min (RIVM, 2006,7) Inhalation uptake of 50% Inhalation rate of 16.2 m^3/day (RIVM, 2006,7) Inhalation model: exposure to vapour by evaporation.	Inhalation mean event concentration: 5.41 x 10^{-2} mg/m^3 Inhalation chronic (internal) dose: 2.2 x 10^{-7} mg/kg/day
		Molecular weight of 86.1 g/mol Vapour pressure of 89.1 mm Hg KOW of 0.7 10Log Adult body weight of 70.9 kg (Health Canada, 1998) Weight fraction of 5 x 10^{-7} or 5 ppm Exposed area of 110 cm^2 (RIVM, 2006,7) Contact rate of 30 mg/min (RIVM, 2006,7) Release duration of 75 min (RIVM, 2006,7) Uptake fraction of 100% Dermal model: direct dermal contact with product at a constant rate.	Dermal acute (internal) dose: 1.59 x 10^{-5} mg/kg Dermal chronic (internal) dose: 1.09 x 10^{-8} mg/kg/day
15	Food packaging	Molecular weight of 86.1 g/ mol Vapour pressure of 89.1 mm Hg KOW of 0.7 10Log Adult body weight of 70.9 kg (Health Canada, 1998) Exposure frequency of 5 x /week (RIVM, 2006,7) Oral model: migration from packaging material, release at constant rate Compound concentration packaging of 0.934 g/cm^3 Thickness of packaging of 25 micrometers Contact area of 10 cm^2 Packaged amount of 50 g Ingested product amount of 50 g Migration rate 0 mg/sec UK Food study Storage time 24 hour Uptake fraction of 100%	Oral acute (internal) dose: 0 mg/kg Oral chronic (internal) dose: 0 mg/kg/day
16	Paint	Molecular weight of 86.1 g/mol Vapour pressure of 89.1 mm Hg KOW of 0.7 10Log Exposure frequency of 1 x / year (RIVM, 2006,7) Adult body weight of 70.9 kg (Health Canada, 1998) Weight fraction of 5.2 x 10^{-6} or 5.2 ppm Exposure duration of 132 min (RIVM, 2006,7) Room volume of 20 m^3 (RIVM, 2006,7) Ventilation rate of 0.6 x /hr (RIVM, 2006,7) Applied amount of 1.25 x 10^3 g (RIVM, 2006,7) Release area of 10 m^2 (RIVM, 2006,7) Application duration of 120 min (RIVM, 2006,7) Mol weight matrix of 45 g/mol (RIVM, 2006,7) Mass transfer rate of 0.297 m/min (RIVM, 2006,7) Uptake fraction of 50 % Inhalation rate of 16.2 m^3/day (RIVM, 2006,7) Inhalation model: exposure to vapour by evaporation where area of release increases over time. Scenario describes the brushing or rolling of a wooden lathed wall in a small room	Inhalation mean event concentration: 1.0 x 10^{-1} mg/m^3 Inhalation chronic (internal) dose: 2.93 x 10^{-6} mg/kg/day

		with low ventilation. Density of waterborne paint of 1.25 g/cm^3)	
		Molecular weight of 86.1 g/mol Vapour pressure of 89.1 mm Hg KOW of 0.7 10Log Adult body weight of 70.9 kg (Health Canada, 1998) Weight fraction of 5.2 x 10^{-6} or 5.2 ppm Exposed area of 0.367 m^2 (RIVM, 2006,7 general fact sheet area for hands and arms) Contact rate of 30 mg/min (RIVM, 2006,7) Release duration of 120 min (RIVM, 2006,7) Dermal uptake of 100% Dermal model: direct dermal contact with product: constant rate	Dermal acute (internal) dose: 2.64 x 10^{-4} mg/kg Dermal chronic (internal) dose: 7.23 x 10^{-7} mg/kg/day
17	Personal wipes	Molecular weight of 86.1 g/mol Vapour pressure of 89.1 mm Hg KOW of 0.7 10Log Exposure frequency of 365 x / year (RIVM, 2006,7) Adult body weight of 70.9 kg (Health Canada, 1998) Weight fraction of 2.4 x 10^{-5} or 24 ppm (90th percentile) Exposed area of 215 cm^2 (RIVM, 2006,7) Applied amount of 0.02 g (RIVM, 2006,7) Uptake fraction of 100% Dermal model: direct dermal contact with product- instant application The worst-case estimate is that 0.1% of the amount on the surface contacts the skin.	Dermal acute (internal) dose: 6.77 x 10^{-6} mg/kg Dermal chronic (internal) dose: 6.77 x 10^{-6} mg/kg/day

APPENDIX III Comparison between model results for WPEM and ConsExpo v4.1 for estimation of exposure from consumer do-it-yourself painting

WPEM Results

Scenario no. 1 (WPEM defaults for a DIY painter)

- $ Lifetime average daily dose (LADD): 4.35 x 10^{-7} mg/kg-days
- $ Average daily dose (ADD): 6.51 x 10^{-7} mg/kg-days
- $ Acute potential dose rate (highest 24-hr dose rate for exposed individual): 1.26 x 10^{-4} mg/kg-days
- $ APDR Time: 1.33 days
- $ Single event dose: 2.28x 10^{-2} mg
- $ Lifetime average daily concentration (LADC): 2.13 x 10^{-6} mg/m^3
- $ Average daily concentration: 3.19 x 10^{-6} mg/m^3
- $ Cpeak= highest instantaneous concentration to which individual is exposed: 2.33 x 10^{-3} mg/m^3
- $ C-15 min: highest 15-min average concentration to which an individual is exposed: 2.31x 10^{-3} mg/m^3
- $ C8-hour: highest 8-hour average concentration to which individual is exposed: 7.86x 10^{-4} mg/m^3

Defaults:

- $ One bedroom painted in 3.42 hours by one DIY painter
- $ Length of run: 20 days
- $ Reporting interval: 60 minutes
- $ Type of Building: House
- $ Air Exchange Rate: 0.45 air changes per hour
- $ Volume: 15583 ft3
- $ Interzonal airflow rate: 3451.63 ft3/hour
- $ Percent painted: 10.0%
- $ Loading ratio: 0.29 ft2/ft3
- $ Painted Surface Area: 451.91 ft2
- $ Coverage: primer 200 ft2/gal; paint 400 ft2/gal
- $ Gallons of paint: 0 for primer, 1.13 for paint
- $ Painting hours: 0 for primer, 3.42 hrs for painting
- $ Work hours: 8 hrs
- $ Painting days: 1
- $ Start day: Monday
- $ Type of paint: Latex, Flat
- $ Density: primer 4600 g/gal; paint 4600 g/gal
- $ Chemical: vinyl acetate monomer
- $ Mol wt: 86.1 g/mol
- $ Vapour Pressure: 89.1 mm Hg
- $ Weight fraction: 5 ppm 90th percentile
- $ Gender: non-specific
- $ Breathing rate during painting: 27.5 m3/day
- $ Lifetime exposure events: 38
- $ Years in lifetime: 75

Scenario no. 2 (ConsExpo defaults)

- $ Lifetime average daily dose (LADD): 4.02 x 10^{-6} mg/kg-days
- $ Average daily dose (ADD): 6.02 x 10^{-6} mg/kg-days
- $ Acute potential dose rate (highest 24-hr dose rate for exposed individual): 2.03 x 10^{-4} mg/kg-days
- $ APDR Time: 1.38 days
- $ Single event dose: 3.33 x 10^{-2} mg
- $ Lifetime average daily concentration (LADC): 2.11 x 10^{-5} mg/m^3
- $ Average daily concentration: 3.16 x 10^{-5} mg/m^3
- $ Cpeak= highest instantaneous concentration to which individual is exposed: 4.63 x 10^{-3} mg/m^3
- $ C-15 min: highest 15-min average concentration to which an individual is exposed: 4.60 x 10^{-3} mg/m^3
- $ C8-hour: highest 8-hour average concentration to which individual is exposed: 1.92 x 10^{-3} mg/m^3

Defaults:

- $ Length of run: 5 days
- $ Reporting interval: 60 minutes
- $ Type of Building: House
- $ Air Exchange Rate: 0.6 air changes per hour ConsExpo v.4.1
- $ Volume: 44000 ft3 (2200 ft2 x 20ft height)
- $ Interzonal airflow rate: 12320 ft3/hour
- $ Percent painted: 1.6%
- $ Loading ratio: 0.61 ft2/ft3
- $ Painted Surface Area: 428 ft2 ConsExpov.4,1
- $ Coverage: primer 334 ft2/gal; paint 334 ft2/gal
- $ Gallons of paint: 1.28 for primer, 1.28 for paint
- $ Painting hours: 8 hrs for primer, 8 hrs for painting
- $ Work hours: 8 hrs for priming, 8 hrs for painting
- $ Painting days: 2
- $ Start day: Saturday
- $ Type of paint: Latex, Semi-gloss
- $ Density: primer 6250 g/gal; paint 6250 g/gal ConsExpo v. 4.1
- $ Chemical: vinyl acetate monomer
- $ Mol wt: 86.1 g/mol
- $ Vapour Pressure: 89.1 mm Hg
- $ Weight fraction: 5 ppm 90th percentile
- $ Gender: non-specific
- $ Breathing rate during painting: 16.2 m3/day ConsExpov. 4.1
- $ Lifetime exposure events: 233
- $ Years in lifetime: 75
- $ Average body weight: 70.9 kg Health Canada, 1988

APPENDIX IV: Summary of health effects information for Vinyl Acetate

Endpoint	Lowest effect levels[3]
Laboratory animals and *in vitro*	
Acute toxicity (i.e. single exposure)	**Inhalation** 4 hour LC_{50} 3680 – 4650 ppm in rats (13000 – 16400 mg/m^3) (Czajkowska et al. 1986; Weil & Carpenter 1969; Smyth & Carpenter 1973) 4 hour LC_{50} 1460 ppm in mice (5140 mg/m^3) (Smyth & Carpenter 1973) 4 hour LC_{50} 2760 ppm in rabbits (9720 mg/m^3) (Smyth & Carpenter 1973) 4 hour LC_{50} 5210 ppm in guinea pig (18300 mg/m^3) (Smyth & Carpenter 1973) Respiratory damage was the cause of death in the rat, mouse, rabbit and guinea pig in these studies. RD_{50} 380 ppm (equivalent to 1338 mg/m^3): concentration inducing a 50% decrease in respiratory frequency of mice following a 30 minute inhalation exposure using method ASTM E981 (Dudek et al. 1996) LO(A)EL = 600 ppm (equivalent to 2110 mg/m^3) based on degeneration/necrosis of olfactory epithelium and increased cell proliferation (BrdU-labelling) of the nasal mucosa in rats exposed for 6 hours to vinyl acetate at nominal air concentrations of 0, 50, 200, or 600 ppm (equivalent to 0, 176, 704, 2110, 3520 mg/m3 calculated using the dose conversion in IARC 1995). The no effect concentration was considered to be 200 ppm by the EU RAR (2008) for these effects. (Bogdanffy et al. 1997) **Oral** LD_{50} 2900 mg/kg-bw (rats) (Smyth & Carpenter 1948) LD_{50} 1600 mg/kg-bw (mice) (Goeva, 1966) **Dermal** LD_{50} 2330 – 7440 mg/kg-bw (rabbits) (converted from 2.5-8 ml/kg bw with density of 0.932 g/ml) (Smyth & Carpenter 1948; Weil & Carpenter 1969) ATSDR (1992) reported that gross lesions were observed in various tissues in this study (congestion of the lungs and liver, mottled spleen and kidney, and prominent liver acini) (Weil & Carpenter 1969)

[3] Unit conversions for air concentrations based on values from IARC (mg/m3 = 3.52 x ppm) unless otherwise noted.

Short-term toxicity (e.g. 4 week/ 1 month study)	**range of Lowest inhalation LO(A)ECs** =528 to 2110 mg/m^3 (150 to 600 ppm) For the lower end of this range, a LO(A)EC of 150 ppm (equivalent to 528 mg/m^3) was identified based on the reported observation of a "treatment related incidence and severity of respiratory distress and hunched posture" in mice (CD1, 5/sex/group) following exposure to nominal air concentrations of 0, 50, 150, 500, or 1000 ppm (equivalent to 0, 176, 528, 1760, or 3520 mg/m^3 calculated using the dose conversion in IARC 1995) for up to 4 weeks (6 hours/day, 5 days/week). The EU RAR (2008) considered 150 ppm to be the LO(A)EC for this study based on local effects in the respiratory tract. [Note: Limitation for this study include a lack of incidence data for the clinical signs of respiratory distress and hunched posture] (Owen 1979a) For the upper end of the range of short-term inhalation LO(A)ECs, an effect level of 2110 mg/m3 (600 ppm) was identified based on histopathologic changes (degeneration/necrosis of olfactory epithelium & nerve bundles, regenerative hyperplasia of olfactory & respiratory epithelium) and increased cell proliferation (BrdU-labelling) in the nasal mucosa of rats (Crl:Cd BR, 5 males/group) following exposure to nominal air concentrations of vinyl acetate of 0, 50, 200, or 600 ppm (equivalent to 0, 176, 704, 2110, 3520 mg/m^3 calculated using the dose conversion in IARC 1995) for 5 or 20 days (Bogdanffy et al., 1997). The EU RAR (2008) has reported 200 ppm as a NO(A)EC for this study based on these effects. (Bodganffy et al. 1997) **Lowest oral LO(A)EL** = 100 mg/kg-bw/day (1000 ppm) Rats (Sprague-Dawley, 5/sex/group) exposed to vinyl acetate in drinking water at concentrations of 0, 50, 200, 1000, 5000 ppm (reported in EU RAR as equivalent to 0, 5, 20, 100, 500 mg/kg-bw/day) for up to 4 weeks were reported to have reductions in body weight gain in females at ≥ 1000 ppm. The EU RAR (2008) considered the NO(A)EL for this study to be 200 ppm based on this effect while it was noted that decreased water consumption may have reflected bad palatability of the test solutions. An observation of reduced liver weights (absolute and relative) in both sexes at all doses was considered to be an equivocal finding by the EU RAR (2008) due to the absence of histopathologic changes. (Gale 1979) [Additional inhalation studies: Gage 1970, Owen 1979b, Bogdanffy et al. 1997, Hurtt et al. 1995] [Additional oral studies: Laib & Bolt 1986, Gale 1979 (mice), Hurtt et al. 1995]

Subchronic toxicity (e.g. 90 day/ 13 week/ 3 month study)	**Lowest inhalation LO(A)EC=** 704 mg/m3 (200 ppm) based on various histopathologic effects and clinical signs of toxicity reported in mice (CD-1, 10/sex/group) following a 3 month inhalation to nominal vinyl acetate exposure concentrations of 0, 50, 200, or 1000 ppm (reported as 176, 704, or 3520 mg/m^3 by IARC (1995) and US EPA (1990)). The 200 ppm exposure concentration has been considered as the lowest effect level for this study based on: focal pneumonitis in the lung and diffuse rhinitis in the nasal cavity (US EPA 1990), inflammation of the nasal turbinate epithelium and mild muti-focal bronchitis (ATSDR 1992), respiratory distress (EU RAR 2008; IARC 1995), and hunched posture (EU RAR 2008). The ATSDR (1992) used the NO(A)EC of 50 ppm from this study for derivation of an intermediate inhalation minimal risk value (MRL). (Owen 1980a) **Lowest oral LO(A)EL**= 38 mg/kg-bw/day (200 ppm) Mice (CD-1, 10/sex/group) were exposed for 3 months to vinyl acetate in the drinking water at concentrations of 0, 200, 1000, or 5000 ppm (reported in ATSDR as equivalent to 0, 38, 190, or 950 mg/kg-bw/day). The ATSDR (1992) considered 200 ppm to be a lowest effect level for this study based on significantly reduced absolute and relative spleen weights for females of the 200 ppm and 1000 ppm groups, However, as no changes in spleen weights were observed for either sex at the highest tested dose of 5000 ppm, and no histopathology of the spleen was observed, the study authors did not consider spleen weight changes to be treatment related. While the ATSDR (1992) noted that spleen weight changes have been reported for other inhalation and oral studies on vinyl acetate, they recognized that these changes were not always dose-related. The EU RAR (2008) reported no exposure related effects for this study and considered the highest tested dose of 5000 ppm to be the NO(A)EL. Given these limitations for spleen weigh changes observed in this study, there is lower confidence level in the LO(A)EL of 38 mg/kg-bw/day (200 ppm) reported by ATSDR (1992). (Gale 1980b) [Additional inhalation studies: Owen 1980b] [Additional oral studies: Clary 1988, Gale 1980a, Mebus et al. 1995, Valentine et al. 2002]
Chronic toxicity/ carcinogenicity (e.g. 104 week /2 year/ 24 month study)	**Inhalation exposure** Groups of male and female rats (60/sex/group, Sprague-Dawley-derived Crl:Cd(SD)BR) were exposed for 104 weeks (6 hours/day, 5 days/week) to nominal vinyl acetate exposure concentrations of 0, 50, 200, or 600 ppm (equivalent to 0, 176, 704 or 2112 mg/m^3 as reported in IARC 1995). An exposure-related increased incidence of nasal tumours was observed in the 600 ppm group of both sexes (0/59, 0/60, 1/59, 7/59 for males, and 0/60, 0/60, 0/60, 4/59 for females in the control, 50, 200, and 600 ppm groups respectively). Tumours in the 600 ppm males consisted of 4 inverted papillomas, 2 squamous cell carcinomas, and 1 carcinoma in situ (total 7/59 was statistically significant $p<0.01$) while the 4 tumours in 600 ppm females were all squamous cell carcinomas ($p=0.06$ as reported in IARC 1995). IARC (1995) considered this study to have demonstrated an increase in nasal cavity tumours in and the EU RAR (2008) considered the tumourigenic LO(A)EC to be 200 ppm NO(A)EC of 50 ppm) based on the observation of an olfactory papilloma in one male rat at 200 ppm with statistically significant increased nasal tumours at 600 ppm. For the neoplastic effects of vinyl acetate by the inhalation route of exposure, the proposed mode of action (MOA) described in the EU RAR (2008) is being considered in this assessment. Therefore a NO(A)EC value of 50 ppm (176 mg/m3) from this study is considered to be the threshold level for neoplastic effects as reported in the EU RAR (2008). Regarding non-neoplastic effects, the study authors reported increased lung weights at 600 ppm and various lesions observed throughout the airway (nasal cavity, trachea, bronchi, alvioli) of the 200 ppm and 600 ppm groups. The non-neoplastic inhalation LO(A)EC of 200 ppm (704 mg/m^3) for this study was based on significant

	increases ($p \leq 0.05$) in nasal cavity lesions of both sexes (atrophy of olfactory epithelium, basal cell hyperplasia) which increased in severity and frequency at the 600 ppm exposure concentration. The no effect level of 50 ppm from this study was used by the US EPA (1990) for the derivation of a chronic inhalation reference concentration (RFC) and by the EU RAR (2008) for the calculation of chronic inhalation margins of safety. (Bogdanffy et al. 1994a, Owen 1988) Groups of male and female mice (60/sex/group, Swiss-derived Crl:CD-1(ICR)BR strain) were exposed for 104 weeks (6 hours/day, 5 days/week) to nominal vinyl acetate exposure concentrations of 0, 50, 200, or 600 ppm (equivalent to 0, 176, 704 or 2112 mg/m^3 as reported in IARC 1995). No treatment-related increase in tumour incidence was reported in any examined tissues. For this study, IARC (1995) and EU RAR (2008) concluded that no treatment-related increase in tumour incidence was observed in mice. The authors reported a squamous cell carcinoma of the lung in 1/59 males in the 600 ppm group but none in the control, 50 ppm, or 200 ppm groups. This tumour was noted by IARC (1995) and EU RAR (2008) but not further commented on. Regarding non-neoplastic effects, the study authors reported changes in the respiratory system including increased lung weights at 600 ppm and various lesions observed throughout the airway (nasal cavity, trachea, bronchi, alvioli) in the 200ppm and 600 ppm groups. A non-neoplastic inhalation LO(A)EC of 200 ppm (704mg/m^3) for this study was based on significant increases ($p \leq 0.05$) in nasal cavity lesions of both sexes (atrophy of olfactory epithelium, submucosal gland hyperplasia, replacement of olfactory with respiratory epithelium in females) which increased in severity and frequency at the 600 ppm exposure concentration. The no effect level of 50 ppm from this study was used by the US EPA (1990) for the derivation of a chronic inhalation reference concentration (RFC) and by the EU RAR (2008) for the calculation of chronic inhalation margins of safety. (Bogdanffy et al. 1994a, Owen 1988) **Oral exposure** Groups of male and female rats (60/sex/group, Sprague Dawley-derived Crl:CD(SD)BR strain) from an F_1 generation of were exposed from gestation (F_0 dam *in utero,* lactation) to 104 weeks to nominal vinyl acetate concentrations of 0, 200, 1000, or 5000 ppm in the drinking water (estimated daily vinyl acetate intake reported by the author to be 0, 10, 47, 202 mg/kg-bw/day in males, 0, 16, 76, and 302 mg/kg-bw/day in females). There were no exposure-related tumours or non-neoplastic lesions reported. For this study, IARC concluded that "no increase in tumour incidence was found for rats administered vinyl acetate in the drinking water *in utero* and then for life" (IARC 1995). A squamous cell carcinoma of the oral cavity was observed in 2/50 high dose males (not significant) while none were found in the control or other two dose groups. The IARC Working Group did not comment on the potential relevance of this tumour to vinyl acetate exposure. However, the EU RAR (2008) concluded that "For reason of possible target organs not being routinely examined and the fact that dose-related and significantly increased tumour rates in this study were absent did not give sufficient proof that carcinogenic potential of vinyl acetate was negative. Even when oral cavity was not examined as a protocol organ, two squamous carcinomas were seen in the high dose males. As squamous cell carcinomas were not seen in control animals and rarely occur in historical control rats of this strain, it comes into question - due the rapporteurs opinion - that this finding may be related to vinyl acetate administration. Assumption is supported by concordance with data from other oral cancer studies in rats and mice that reported squamous cell carcinomas in the oral cavity (Umeda et al. 2004a)". Regarding non-neoplastic effects, there was a statistically significant decrease ($p \leq 0.05$) in water intake reported for both sexes of the 1000 and 5000 ppm groups during the first year and in the high group in the second year. The high dose group displayed significant decreases in body weight gains (both sexes) and food consumption (males only) especially in the second year of the study.

	Some observed changes in organ weights in the high dose group were attributed by the study authors to the decreased body weights rather than vinyl acetate exposure. The EU RAR (2008) considered 202 mg/kg-bw/day (5000 ppm) as the non-neoplastic oral LO(A)EL this study is based on decreased body weights in the 5000 ppm group, however it should be noted that decreased water intake and food consumption was also reported at 5000 ppm. (Bogdanffy et al. 1994b) Groups of male and female mice (Swiss strain) were exposed for 78 weeks to vinyl acetate in drinking water at nominal concentrations of 0, 1000, or 5000 ppm (equivalent to 0, 200 or 1000 mg/kg-bw/day using a dose conversion from Health Canada 1994). Exposure started either at 17 weeks of age (F_0 breeders) or from gestational day 12 (F_1 offspring) and continued for 78 weeks and were kept under control conditions until spontaneous death. The animal numbers varied somewhat between the treatment groups of the F_0/F_1 and treatment groups (13-14 males & 37 females/group in the F_0, 37-49 males and 44-48 females/group in the F_1). Overall, the authors reported an increased incidence of squamous cell carcinomas in tissues of the upper gastro-intestinal tract (GIT) in mice of the 5000 mg/L group. No statistical analysis was performed in the paper, therefore the greatest reported differences between control and exposure group frequencies of squamous cell carcinoma or squamous cell dysplasia are as follows for the 5000 ppm group: oral cavity (carcinoma in 10/49 F_1 males and 9/48 F_1 females), esophagus (carcinoma in 6/37 F_0 females, 12/49 F_1 males, 18/48 F_1 females; dysplasia in 4/13 F_0 males, 6/37 F_0 females, 4/49 F_1 males, 7/47 F_1 females), forestomach (carcinoma in 3/37 F_0 females, 2/49 F_1 males, and 7/48 F_1 females). No exposure-related effects in the upper GIT were reported at the 1000 ppm exposure level. The LO(A)EL for squamous cell dysplasia of the upper GIT in this study is considered to be 1000 mg/kg-bw/day (5000 ppm) based on increased frequencies above the control group in the esophagus of both sexes of the F_0 and F_1. The EU RAR (2008) considered a "clear tumour response" to have been demonstrated at 5000 ppm based on increased incidence of squamous cell tumours of the gastrointestinal tract. Other types of tumours (lung, liver, uterus, etc.) were observed in this study, however the EU RAR (2008) reported that these findings were not consistent with findings in Umeda et al. (2004). In addition, the EU RAR (2008) noted that high spontaneous occurrence of these tumours in the control group of this study make the interpretation difficult. [Note some study limitations: reporting for some data was limited (food & water intake, clinical observations, statistical analysis, etc. were not presented), no reporting of historical control tumour incidence, use of a non-standard cancer bioassay design (exposure duration less than 2 years, animals observed until natural deaths, recovery period after exposure duration, exposure during pregnancy/in utero for a portion of the study)] (Maltoni et al. 1997) Groups of male and female rats (Sprague-Dawley strain) were exposed for 104 weeks to vinyl acetate in drinking water at nominal concentrations of 0, 1000, or 5000 ppm (equivalent to 140 or 700 mg/kg-bw/day using a dose conversion from Health Canada 1994). Exposure started either at 17 weeks of age (F_0 breeders) or from gestational day 12 (F_1 offspring) and continued for 104 weeks and were kept under control conditions until spontaneous death. The animal numbers varied somewhat between the treatment groups of the F_0/F_1 and treatment groups (13 males & 37 females/group in the F_0, 53-107 males and 57-99 females/group in the F_1). Overall, the authors reported a significant ($p<0.01$ Chi^2 test) dose-dependent increase in the combined incidence of squamous cell carcinomas and squamous cell dysplasia in tissues of the upper gastro-intestinal tract (GIT). The study authors reported the significant increases in upper GIT squamous cell carcinomas in the following groups: oral cavity & lips of F_1 males (13/53) and females (9/57) in the 5000 ppm group, forestomach of F_1 males (7/53) and females (4/57) of the 5000 mg/L group, and forestomach of the F_1 males (6/83) of the 1000 ppm group. The incidence of squamous cell carcinomas observed in the control F_1 group was 3/206 animals. The authors also reported squamous cell dysplasia

	(considered an oncological precursor lesion by the study authors) to be significantly increased ($p<0.05$ by Chi^2 or $p<0.01$ by Cochrane-Armitage trend test) in GIT tissues of the 5000 ppm group (tongue of F_0 and F_1 females, esophagus of F_0 and F_1 females and F_1 males, forestomach of F_1 males and females) and 1000 ppm group (tongue of F_1 females, esophagus of F_0 and F_1 females, and forestomach of F_1 males and females). The LO(A)EL for squamous cell dysplasia of the upper GIT in this study is considered to be 140 mg/kg-bw/day (1000 ppm). The EU RAR (2008) considered squamous cell dysplasia to be increased in both F_0 and F_1 groups at the 5000 ppm concentration. Note that the study authors reported significant increases in upper GIT squamous cell carcinomas at the same concentration of 1000 ppm. The EU RAR (2008) considered a "clear tumour response" to have been demonstrated at 1000 ppm for the F_1 males in the forestomach and at 5000 ppm for both sexes of F_1 offspring in the oral cavity and forestomach. [Note some study limitations: reporting of some data was limited (survival, body weight, food & water intake, clinical observations, etc. were not presented), no reporting of historical control tumour incidence, and use of a non-standard cancer bioassay design (animals observed until natural death, recovery period after exposure duration, exposure during pregnancy/in utero for a portion of the study)] (Minardi et al. 2002) Groups of male and female rats (Wistar strain) were exposed for 104 weeks to vinyl acetate in drinking water at nominal concentrations of 0, 1000, or 5000 ppm (equivalent to 0, 140 or 700 mg/kg-bw/day using a dose conversion from Health Canada 1994). Exposure started either at 17 weeks of age (F_0 breeders) or from gestational day 12 (F_1 offspring) and continued for 104 weeks and were kept under control conditions until spontaneous death. The animal numbers varied somewhat between the treatment groups of the F_0/F_1 and treatment groups (13 males & 37 females/group in the F_0, 64-86 males and 69-95 females/group in the F_1). Overall, the authors reported a dose-dependent increase in the combined incidence of squamous cell carcinomas and squamous cell dysplasia in tissues of the upper gastro-intestinal tract (GIT) which was significant in both sexes at 5000 ppm ($p<0.01$ Chi^2 test), at 1000 ppm groups for F_0 females ($p<0.05$ Chi^2 test), and in male and female F_1 and F_0 ($p<0.01$ by Cochrane-Armitage trend test). However, statistical analysis of tumour incidence in the individual GIT tissues revealed the only significant increase to be for squamous cell carcinomas in the oral cavity at 5000 ppm (12/82 males $p<0.05$ and 24/95 females $p<0.01$ of F_1, by Chi^2 test) and a positive trend at 1000 ppm (11/73 F_1 females, $p<0.01$ by Cochrane-Armitage trend test). The study authors concluded the other GIT tissues (tongue, esophagus, forestomach) also displayed increases of squamous cell carcinomas in the 5000 ppm F_1 males and females, though the differences were not statistically significant. The authors also reported squamous cell dysplasia (considered an oncological precursor lesion by the study authors) to be significantly increased (p at least <0.05 by Chi^2) in GIT tissues of the 5000 ppm group (oral cavity of F_1 females, esophagus of F_1 males & females). The LO(A)EL for squamous cell dysplasia of the upper GIT in this study is considered to be 700 mg/kg-bw/day (5000 ppm). Note that the study authors reported significant increases in upper GIT squamous cell carcinomas at the same concentration of 5000 ppm. The study authors also reported the number of malignant tumours of the uterus was increased in breeders of both treated groups and in the high dose F_1. The EU RAR (2008) report that other types of tumours, including uterine tumours, were observed in another study (Maltoni et al. 1997), however EU RAR report that these results were not consistent with findings in Umeda et al. (2004). [Note some study limitations: reporting of some data was limited (food & water intake, clinical observations, etc. were not presented), no reporting of historical control tumour incidence, and the use of a non-standard cancer bioassay design (animals observed until natural death, recovery period after exposure duration, exposure during pregnancy/in utero for a portion of the study)] (Belpoggi et al. 2002) Groups of male and female rats (50/sex/group, F344/DuCrj strain) were exposed for 104 weeks to nominal VA concentrations of 0, 400, 2000, or 10000 ppm in the

drinking water (estimated daily vinyl acetate intake reported by the author to be: 0, 21, 98, 442 mg/kg-bw/day in males, and 0, 31, 146, 575 mg/kg-bw/day in females). An increased incidence ($p \leq 0.05$ by Fisher's exact test or Peto's trend test) of squamous cell carcinomas were reported in the oral cavity of both sexes (5/50 males, 3/50 females) of the 10000 ppm group. Other squamous cell tumours were reported in the same tissues in the vinyl acetate groups: oral cavity (papilloma in 2/50 of the 10000 ppm males, squamous cell carcinoma in 1/50 and 1/50 of the 400 ppm and 2000 ppm females), esophagus (carcinoma in 1/50 of the 10000 ppm females). The study authors also reported significant increases ($p<0.05$ by Chi^2 test) of basal cell hyperplasia (classified as pre-neoplastic lesions by the study authors) in the esophagus (4/50) and stomach (5/50) of females in the 10000 ppm group. The study authors reported a significant increase of squamous cell carcinomas at 10000 ppm and a low incidence of this tumour at lower concentrations. The EU RAR (2008) considered the tumourigenic LO(A)EL to be 400 ppm for this study ("weak or questionable tumour response") while a "clear tumour response" was considered to be demonstrated at 10000 ppm. In addition, the EU RAR (2008) noted that a clear threshold for carcinogenicity was not established since 400 ppm was the lowest tested dose. [Note: The authors reported that some decomposition of vinyl acetate (72-80% of target concentrations) to acetaldehyde and acetic acid occurred. As a result, the drinking water of the treatment groups was more acidic than expected (pH 3.6-4.0)]
(Umeda et al. 2004)

Groups of male and female mice (50/sex/group, Crj:BDF_1 strain) were exposed for 104 weeks to nominal VA concentrations of 0, 400, 2000, or 10000 ppm in the drinking water (estimated daily vinyl acetate intake reported by the author to be: 0, 42, 202, 989 mg/kg-bw/day in males, and 0, 63, 301, 1418 mg/kg-bw/day in females). An increased incidence ($p \leq 0.05$ by Fisher's exact test or Peto's trend test) of squamous cell tumours (carcinoma & papilloma) was reported in the upper digestive tract of the 10000 ppm group and considered by the study authors to be exposure-related: oral cavity (4/50 male & 3/50 female papilloma, 13/50 male & 15/50 female carcinoma), esophagus (7/50 male carcinoma), forestomach (7/50 male & 3/50 carcinoma). The study authors also reported an increased frequency (p at least <0.05) of effects in the stratified squamous epithelium (classified as pre-neoplastic lesions by the study authors) of the upper digestive tract in the 10000 ppm group: oral cavity (basal cell and squamous cell hyperplasia and epithelial dysplasia in both sexes), esophagus (basal cell hyperplasia in both sexes, epithelial dysplasia in females), forestomach (squamous cell hyperplasia in females), larynx (basal cell hyperplasia in females). The EU RAR (2008) considered a dose-dependent increased incidence of hyperplastic changes in the oral cavity in male and female mice at ≥ 2000 ppm to be a non-neoplastic lowest effect level. The EU RAR (2008) also considered a "weak or questionable tumour response" to be at 2000 ppm while statistically significant squamous cell tumours were observed at 10000 ppm in this study. [Note: The authors reported that some decomposition of vinyl acetate (72-80% of target concentrations) to acetaldehyde and acetic acid occurred. As a result the drinking water of the treatment groups was more acidic than expected (pH 3.6-4.0)]
(Umeda et al. 2004)

The authors of the above two studies concluded that a dose-related increase in the incidence of malignant tumours (squamous cell carcinoma) occurred in the upper digestive tract of two rodent species of both sexes orally administrated VA for 2 years (Umeda et al. 2004)

Lowest inhalation LO(A)EC = 704 mg/m^3 (200 ppm) based on histopathologic changes of the nasal cavity and respiratory tract of mice and rats following a 2yr exposure (Bogdanffy et al. 1994a, see the study description above for details)

range of Lowest oral LO(A)ELs = 31 – 202 mg/kg-bw/day based on several drinking water studies in mice and rats (see the study descriptions above for details):

	- oral cavity tumours in female rats at 400 ppm (31 mg/kg-bw/day) (Umeda et al. 2004) - hyperplastic changes in the oral cavity in male and female mice at ≥ 2000 ppm (202 mg/kg-bw/day) (Umeda et al. 2004) - reduced body weight in males rats 5000 ppm (202 mg/kg-bw/day) (Bogdanffy et al. 1994b) [Additional inhalation studies: Czajkowska et al. 1986; Maltoni et al. 1974] [Additional oral studies: Lijinsky & Reuber 1983; Lijinsky 1988]
Reproductive and Developmental toxicity	**Lowest inhalation LO(A)EC**= 1000 ppm (3520 mg/m^3) based on significant decreases in mean fetal weight and mean crown rump length as well as statistically significant increased frequencies of some skeletal alterations in fetuses of pregnant rats (Crl:CD(SD)BR strain) exposed for 6 hours/day during gestational days 6-15 to nominal vinyl acetate concentrations of 0, 50, 200, or 1000 ppm (equivalent to 0, 176, 704, or 3520 mg/m^3 using the dose conversion from IARC 1995). The EU RAR (2008) considered the 1000 ppm concentration to adversely effect the dam and coneptus with the no effect level being 200 ppm. It should be noted that maternal toxicity was reported (reductions in maternal body weights & weight gain, congestion of the lungs) during at the 1000 ppm concentration (EU RAR 2008). [Note: although the study authors report results for several "reproductive paramaters", the exposure period used in this study (GD5-16) is considered to study developmental toxicity during the period of major embryo organogenesis by others (Hood 2006) and therefore more appropriate for developmental endpoints.] (Hurtt et al. 1995) **Lowest oral LO(A)EL**= 700 mg/kg-bw/day (5000 ppm) based on results of a 2-generation reproductive toxicity study in rats (Crl:CD(SD)BR strain) exposed to nominal vinyl acetate concentrations of 0, 200, 1000, or 5000 ppm (actual intake varied throughout the study so the following equivalents are presented based on a dose conversion from Health Canada 1994: 0, 28, 140, or 700 mg/kg-bw/day). The study authors reported various effects in the 5000 ppm group: reduced fertility in the F_1 , decreased mating performance in the F_1 males when cross-mated with control females, and a significant decrease in body weight of F_1 pups reported on post-partum day 21. The study authors reported 1000 ppm to be the NO(A)EL for this study and is supported by similar conclusions of IARC (1995) and US EPA (1990). [Note: decreases in water consumption and body weights were also reported for males and females of the F_0 and F_1 generations during the study.] (Mebus et al. 1995) [Additional inhalation studies: none identified] [Additional oral studies: Hurtt et al. 1995]

Genotoxicity and related endpoints: *in vitro* (all cited from IARC 1995, unless otherwise noted)

Endpoint	**Results and Reference**			
Gene Mutation	**Species, Strain**	**Result**	**Metabolic Activation**	**Reference**
	mouse lymphoma L5178Y cells	Positive	-	Kirby 1983 (cited in BUA 1994 and ECETOC 1991)
	Salmonella typhimurium TA 97	Negative	+/-	Brams et al. 1987
	Salmonella typhimurium TA 98	Negative	+/-	Lijinksky and Andrews 1980 McCann et al. 1975 Brams et al. 1987 Florin et al. 1980

	Salmonella typhimurium TA100	Negative	+/-	Lijinksky and Andrews 1980 McCann et al. 1975 Brams et al. 1987 Florin et al. 1980 Bartsch et al. 1979
	Salmonella typhimurium TA1530	Negative	+/-	Bartsch et al. 1979
	Salmonella typhimurium TA1535	Negative	+/-	Lijinksky and Andrews 1980 McCann et al. 1975 Florin et al. 1980
	Salmonella typhimurium TA1537	Negative	+/-	Lijinksky and Andrews 1980 McCann et al. 1975 Florin et al. 1980
	Salmonella typhimurium TA1538	Negative	+/-	Lijinksky and Andrews 1980
	Escherichia coli PQ37	Negative	+/-	Brams et al. 1987
Sister Chromatid Exchange	**Positive:** Chinese hamster CHO (+/-S9) (Norppa et al. 1985) Human lymphocytes in vitro (without activation) (Norppa et al. 1985; He & Lambert 1985; Sipi et al. 1992)			
Chromosomal Aberrations	**Positive:** Human lymphocytes in vitro (without activation) (Norppa et al. 1985; Jantunen et al. 1986)			
Micronucleus Induction	**Positive:** Human lymphocytes in vitro (without activation) (Maki-Paakkanen & Norppa 1987)			
DNA-protein cross-links	**Positive:** E. coli HB 101 pUC13 (with activation) (Kuykendall & Bogdanffy 1992) **Negative:** E. coli HB 101 pUC13 (without activation) (Kuykendall & Bogdanffy 1992)			
DNA cross-links	**Positive:** Rat olfactory epithelial cells (without activation) (Kuykendall et al. 1993) Rat nasal epithelial cells (without activation) (Kuykendall et al. 1993) Human lymphocytes (without activation) (Lambert et al. 1985)			
Cell Transformation	**Positive:** Syrian hamster embryo cells (without activation) (Casto 1981)			
Genotoxicity and related endpoints: *in vivo*				
Endpoint	**Results and Reference**			
Micronucleus Induction (bone marrow)	**Positive:** Mouse (i.p.) (Maki-Paakkanen & Norppa 1987, cited in IARC 1995; NTP 1999) **Negative:** Mouse & Rat (drinking water) (Gale 1979, cited in ATSDR 1992 as Hazleton 1979d) Mouse & Rat (inhalation) (Owen 1979a, b, 1980a, b, cited in ATSDR 1992 as Hazleton 1979b,c and Hazleton 1980b,c respectively)			
Chromosomal Aberrations (bone marrow)	**Positive:** Rat (i.p.) (Nersesyan et al. 1990, cited in BUA 1994)			
Meiotic Micronucleus Induction	**Negative:** Mouse (i.p.) (Lahdetie 1988, cited in IARC 1995)			
Sister Chromatid Exchange (bone marrow)	**Positive :** Mouse (i.p) (Takeshita et al. 1986, cited in IARC 1995)			

Sperm morphology	**Positive:** F1 Mice (i.p.) (Lahdetie 1988, cited in IARC 1995)
DNA adducts (covalent binding)	**Negative:** Rat hepatocytes (inhalation, oral) (Simon et al. 1985, cited in IARC 1995)
Humans	
Controlled human exposure	In a series of studies sponsored by Union Carbide, three to nine human volunteers were exposed to vinyl acetate for 2 minutes up to 4 hours at concentrations from 0.6 – 72 ppm (equivalent to 2 – 253 mg/m^3). There is limited reporting of the study design however, it was noted by the study authors that exposure concentrations were unknown to the subjects, presented in random order, and symptoms from individuals were recorded privately. Further details for this study are reported in NIOSH (1978). The 2 minute exposures involved nine subjects exposed twice to concentrations of 0.6, 1.3, 4, 8 or 20 ppm (no indication of wash-out period between repetitions or different exposure concentrations). All nine subjects detected vinyl acetate odour from 1.3 – 20 ppm but not at the lowest concentration of 0.6 ppm while minimal irritation of the eye, nose and throat were reported at ≥ 4 ppm (1/9 at 4 and 20 ppm, 2/9 at 8 ppm). The longer exposures (30 minutes to 4 hours) to concentrations of 20 – 72 ppm were conducted on four consecutive days with the same 3 – 4 volunteers used for all exposures. Throat irritation was reported at all concentrations: 20 ppm (1/3 "slight persistent"), 34 ppm (1/3 "slight persistent", 1/3 "transient"), and 72 ppm (2/4 "slight", 1/4 "slight persistent", 1/4 "dryness of throat"). Eye irritation was also reported for 3/4 subjects at 72 ppm while not observed at the lower two concentrations. From the symptoms reported in this study, a range of LO(A)ECs from 4 – 34 ppm (equivalent to 14 – 120 mg/m^3) have been identified. There is higher confidence in the upper end of this range of LO(A)ECs since the effects reported were more pronounced at 34 ppm. From this study, the US EPA proposed 20 ppm (LO(A)EC of 34 ppm) to represent a "no-effect level for notable discomfort" as the point of departure for derivation of an interim Acute Exposure Guideline Level (AEGL-1) (US EPA 2006b). (Smyth & Carpenter 1973)
Observational studies	During air sampling for vinyl acetate in a Union Carbide chemical plant, subjective responses (odour detection, irritation of eye and upper respiratory tract) were reported in up to five subjects in one of three vinyl acetate production units. For each of the production units being sampled, subjective responses from three individuals were recorded; two responses were from the study author and a lab analyst while the third subject included a worker from the respective production unit being sampled. The vinyl acetate concentrations in the three production units sampled ranged from 0.4 – 21.6 ppm (equivalent to 1 – 76 mg/m^3). Vinyl acetate odour was recorded as "slight" in 2/3 subjects as low as 0.4 ppm, while at a concentration of 21.6 ppm all three individuals reported the vinyl acetate odour as "marked" with eye irritation recorded as "intolerable for extended periods". Also at 21.6 ppm, 2/3 individuals reported a "slight cough" (study author & production unit worker), while 2/3 also reported "slight" hoarseness (lab analyst & production unit worker). At lower measured concentrations only the study author reported any effects ("slight" eye irritation at 5.7-6.8 ppm and "slight" hoarseness at 4.2-5.7 ppm but not at any other higher concentrations until 21.6 ppm). Based on this data, the study authors concluded that vinyl acetate is not a significant irritant to the eye or upper respiratory tract at levels of 10 ppm (next lowest conc. measured after 21.6 ppm). NIOSH (1978) considered 4.2 ppm (15 mg/m^3) to be the lowest concentration reported to induce any irritant effect in this study as the basis for an occupational permissible exposure limit. [Limitations of this study include co-exposure to other chemicals which were not measured and no indication of exposure duration though the US EPA (2006b) considered that exposures were likely of a 10 minute duration. The US EPA also emphasized that these were not controlled exposures (US EPA 2006b)] (Deese & Joyner 1969) Cohort Study: US plant for the manufacture of synthetic chemicals

	4806 men employed between 1942-1973 Exposure of the cohort with lung cancer to 19 chemicals including vinyl acetate was examined and it was estimated that the cumulative dose of exposure to vinyl acetate below the estimated weighted mean expected for members of the cohort with the same year of birth and age at commencement of work in the plant. Observations: Cohort had an excess risk from cancer of the respiratory system in comparison with national rates (42 Observed; standardized mortality ratio 1.5 95% conf. interval, 1.1-2.0) (note death certificates could not be found for 16 (3%) of the deceased. Review of medical records: 45 with lung cancer; 27 of which had histological specimens of which 8 showed undifferentiated large-cell lung cancer. The subgroup with the undifferentiated large-cell lung cancer had a slightly higher cumulative exposure to vinyl acetate. (Waxweiler et al. 1981) Nested case control study in a cohort of 29139 men employed in two large chemical manufacture facilities and a R&D center in the US, who had died in between 1940 and 1978 with non-Hodgkin's lymphoma, multiple myeloma, lymphocytic leukaemia or non-lymphocytic leukemia as the underlying or contributing cause of death. Controls: frequency matched to the cases by date of hire and length of survival in a 5:1 ratio. Exposure to 21 chemicals assessed on basis of information about work activity, work area and production over time. Potential exposure to vinyl acetate reported for 7/52 men who died with non-Hodgkin's lymphoma (OR 1.2); 2/30 with multiple myeloma (OR 1.6); 2/39 non-lymphocytic leukaemia (OR 0.5) and 2/18 with lymphocytic leukemia (OR 1.8). (Ott et al. 1989) In a study conducted by Shirinian & Arutyunyan (1980), occupational exposure to vinyl acetate was reported to be associated with an increased frequency of chromosomal aberrations in cultured lymphocytes. [The IARC Working Group noted the inadequate reporting of the study] (Shirinian & Arutyunyan 1980)