VINYL ACETATE

CAS No: 108-05-4

EINECS No: 203-545-4

SUMMARY RISK ASSESSMENT REPORT

Final report, 2008

Germany

FINAL APPROVED VERSION

Rapporteur for the risk assessment of vinyl acetate is Germany

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PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substance vinyl acetate that has been prepared by Germany in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances.

For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references the reader is referred to the comprehensive Final Risk Assessment Report (Final RAR) that can be obtained from the European Chemicals Bureau[1]. The Final RAR should be used for citation purposes rather than this present Summary Report.

[1] European Chemicals Bureau – Existing Chemicals – http://ecb.jrc.it

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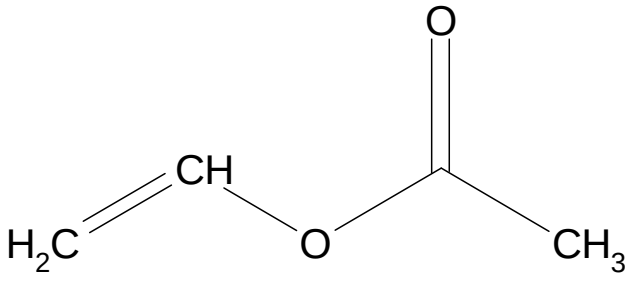
1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS Number: 108-05-4
EINECS Number: 203-545-4
IUPAC Name: vinyl acetate
Synonyms: acetic acid vinyl ester
Molecular weight: 86 g/mol
Molecular formula: $C_4H_6O_2$
Structural formula:



1.2 PURITY/IMPURITIES, ADDITIVES

Purity: 99.8 % w/w

Impurities: ≥ 0.03 - 0.1 % w/w water

≥ 0.005 - 0.01 % w/w acetic acid

≥ 0.005 - 0.02 % w/w acetaldehyde

Additives: hydrochinone or hydrochinone mono methyl ether as stabilisator

0.00015 - 0.002 % w/w

1.3 PHYSICO-CHEMICAL PROPERTIES

Table 1.1 Summary of physico-chemical properties

Property	Value
Physical state	liquid at 20°C
Melting point	- 93.2 °C
Boiling point	+ 72.7 °C
Relative density	0.932 at 20 °C
Vapour pressure	120 hPa at 20 °C
Water solubility	20 g/L at 20 °C
Partition coefficient n-octanol/water (log value)	log Pow 0.7
Flash point	- 8 °C (DIN 51755)
Autoflammability	385 °C (DIN 51794)
Explosive properties	not explosive
Oxidizing properties	not oxidizing
Surface tension	24 mN/m at 20 °C (pure substance)

1.4 CLASSIFICATION

- (Classification according to Annex I, 19th ATP)

F R 11 Highly flammable

- (Proposal of the rapporteur)

The current classification included in Annex I to Directive 67/548/EEC is only due to human health effects and does not yet consider environmental effects of vinyl acetate. Based on the data presented in the environmental section of this risk assessment report and the criteria of Directive 93/21/EEC, the rapporteur proposes the substance not to be classified and labelled for environmental risks.

The classification included in Annex I to Directive 67/548/EEC does not yet include toxic effects. According to the data presented below and the criteria of Directive 93/21/EEC, vinyl acetate should be classified as follows and assigned the risk phrases:

Harmful	R 20	Harmful by inhalation
Irritant	R 37	Irritating to respiratory system
Carcinogenic, Cat. 3	R 40	Limited evidence of a carcinogenic effect

Human data on irritation/corrosion caused by vinyl acetate are not available. In the only valid test (RCC, 2003) mild irritative effects on the skin of rabbits was observed that do not need classification. The eye irritation potential of the compound seems to be mild as judged on the basis of poorly documented eye irritation tests with rabbits. Hence, no classification for eye irritative effects is needed.

Acute inhalation tests with rats demonstrated severe irritation in the respiratory tract of the animals. Thus, vinyl acetate should be labelled “R 37 Irritating to respiratory system”.

Results from an animal skin sensitization study (Buehler Test) showed a moderate skin sensitising potential of vinyl acetate (commercial grade). With the use of the Local Lymph Nodes Assay (LLNA) no significantly positive stimulation responses were detected at concentrations of 5% - 100%. Overall, the outcome of both studies may indicate that vinyl acetate is not devoid of a skin sensitising potential. The results of the LLNA do confirm the weak-moderate effects seen in the Buehler test. However, since the positive threshold level was not exceeded in the LLNA, classification and labelling with R 43 is not warranted.

There is clear evidence for the carcinogenicity of vinyl acetate in two animal species and in both sexes. The carcinogenic potential was demonstrated for the inhalation and oral route of administration. Vinyl acetate exposure produced tumors at the site of first contact along the exposure routes. A thresholded mode of carcinogenic action is thought to be active. The observed tumor responses are reflecting the target site-specific enzyme activities:

Following inhalation and oral exposure vinyl acetate is rapidly hydrolysed by carboxylesterases leading to the formation of acetic acid and acetaldehyde which is further converted into acetic acid in the presence of aldehyde dehydrogenases. Intracellular aldehyde dehydrogenase activity is limited, at higher concentrations of vinyl acetate it will not be sufficient for the oxidation of generated acetadehyde. Thus, at high vinyl acetate concentrations non-physiological concentrations of acetaldehyde are produced. Acetaldehyde is a physiological intermediate with low background concentrations. Its adverse effects (genotoxicity and mutagenicity) are limited to non-physiologically high concentrations. Therefore, a threshold mode of action is assumed for vinyl acetate.

Above threshold concentrations, cytotoxicity (only at the olfactory mucosa), mitogenic actions and genotoxic actions occurred.

Data on vinyl acetate are in line with the idea that vinyl acetate genotoxicity is mediated by acetaldehyde. Increasing concentrations of acetaldehyde produce genotoxic actions at the site of contact. It has to be taken into consideration that acetaldehyde occurs naturally in mammalians cells and is part of the physiological cellular metabolism.

From animal data it is concluded that vinyl acetate might pose a cancer risk for humans exposed to the substance via the inhalation or oral route. Carcinogenicity is thought to act via a secondary mechanism and the concern may only be relevant above threshold concentrations. The observed effects are thought to be relevant for the human. For the respiratory tract humans may be less sensitive than the rat due to a lower carboxylesterase activity in the nasal mucosa.

In Germany, vinyl acetate is assigned to the MAK-pregnancy category "D" denoting that the current data base is not sufficient for final evaluation of developmental toxicity. However it is outlined that vinyl acetate was evaluated for reproductive toxicity in one species (rat) already

with negative results. If this latter outcome could be verified in additional species vinyl acetate could be assigned to category "C" denoting that no risk for adverse developmental effects have to be expected for female workers in compliance with the respective MAK value of 10 ppm.

2 GENERAL INFORMATION ON EXPOSURE

Production

Vinyl acetate is produced by a catalytic vapour-phase reaction of ethylene and acetic acid in gas phase, liquid phase or a fluidised-bed process. Five producers of vinyl acetate monomer (VAM) were identified in Western Europe with a nominal production capacity of 800,000 t/a (CEFIC). Fluctuating operating rates make it difficult to provide a general figure for the annual production volume of VAM in the EU.

From the total supply of about 1,045,000 tonnes, some unquantified amounts were exported outside Western Europe again (figures were not given by industry for confidentiality reasons). With an end stock[2] of less than 50,000 tonnes in 2002, approximately 750,000 tonnes of VAM were marketed in Western Europe that year (all figures provided by CEFIC Acetyls Sector Group).

Uses

Vinyl acetate monomer is solely used as an intermediate in chemical industry for manufacturing (polymerisation) of vinyl acetate (co)polymers. Hence it is concluded that the entire production volume of VAM is used up for the manufacture of various (co)polymers, mainly polyvinyl acetate. Apart from manufacture of homopolymers the monomer is combined with other monomers like ethylene, vinyl chloride and acrylic acid esters to form various types of co-polymers.

Polymers manufactured from VAM are used in a broad spectrum of products, including water-based paints, printing inks, lacquer, ceramic, adhesives for packaging and construction, paper finishing, and protective colloids for various materials. Other important products include textile fibres, paper coating and inks.

The content of residual VAM in homo- and co-polymers depends on the product, spanning a wide range of reported values of less than 5 ppm up to 6,000 ppm. A quantitatively weighted median value for the monomer content of roughly 3,000 ppm is given in the literature. The latter value is used for estimating diffuse releases of VAM from (co)polymers and end-use products.

In addition, vinyl acetate (co)polymers are used as feedstock for manufacture of vinyl alcohol (co)polymers (e.g. polyvinyl alcohol). Polyvinyl alcohol is obtained by hydrolysing polyvinyl acetate. The production capacity within the EU is reported to be > 100,000 t/a. Commercial grades of polyvinyl alcohol differ in the degree of polymerisation (molecular mass) and degree of hydrolysis (residual polyvinyl acetate content). Along with saponification (alkaline hydrolysis of fatty acid esters) of the acetyl moieties of polyvinyl acetate, monomer residuals are getting eliminated as well. A minor fraction of polyvinyl alcohol ends up in the manufacture of polyvinyl acetales, e.g. of polyvinyl butyral (PVB).

A broad quantitative breakdown of the use pattern of vinyl acetate is available for Germany for 1990. In this year, approximately 68 % of the produced vinyl acetate was used mainly for the manufacturing of polyvinyl acetate and, to a less extent, for the manufacturing of

[2] Closing or end stock of the previous period. Includes all product produced or purchased but not yet invoiced or transferred to internal captive use, e.g. product in storage points or products in transit.

copolymers. 32 % of the produced vinyl acetate was manufactured to polyvinyl alcohol. Vinyl acetate occurs as residual monomer in homo- and copolymers based on vinyl acetate and in products or formulations based on these polymers. As polyvinyl alcohol is produced by trans esterfication (saponification) of vinyl acetate (co)polymers, residual vinyl acetate monomer does not occur in polyvinyl alcohol and in polymers derived from polyvinyl alcohol. Hence the manufacturing of polyvinyl alcohol is not relevant in the context of residual monomer content.

The amounts of VAM processed in the EU were assessed using two different approaches based on single site information and market statistics, respectively. Site specific information was gathered by CEFIC by means of a questionnaire. It is concluded that the data provided on production and processed volumes of VAM do not match very well:

	Based on single sites:	**Based on market statistics :**
Production	800,000 tonnes	715,000 tonnes
Processing	474,900 tonnes	750,000 - 800,000 tonnes (estimate)

The maximal difference between reported production volume and specific processing data for individual sites is 325,000 t/a (= 800,000 t/a - 475,000 t/a). It is therefore assumed that a number of processing sites exist that were not covered by the CEFIC questionnaire. As no information on these sites is available, a generic risk characterization is conducted. The estimated total emissions that are released during processing of the total volume of 325,000 t/a are included in the calculation of the regional and continental background concentrations.

Specific local risks were calculated for the production and processing sites that could be identified. In several cases it could not be clarified whether the term “use” in the questionnaire was interpreted by the responders as (co)polymerisation, or compounding of already polymerised material, or both. If not specified otherwise it was assumed that the data referred to (co)polymerisation, although this may overestimate emissions in some cases. Five producers of VAM were identified being located in four EU member states (France, Germany, Spain and UK). Identified processing plants are located in Belgium, Denmark, Finland, France, Italy, Germany, the Netherlands, Spain and UK. No information on geographical locations was disclosed by industry associations that provided only aggregated data.

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

Environmental releases

Vinyl acetate is used as an intermediate in the production of a range of polymeric materials. Releases of the monomer into the environment may be expected during various life cycle stages and from the final products and articles generated from VAM. VAM is a comparatively volatile substance that is likely to evaporate into the atmospheric compartment, primarily via off-gas. Likewise, owing to the high water solubility of VAM, emissions may occur to the aqueous phase if the substance is getting into contact with water. Waste water may in turn be a relevant source for emissions to the atmosphere during treatment (e.g. stripping).

Environmental fate

VAM undergoes rapid photooxidative transformation in air.

VAM undergoes hydrolysis in surface and groundwater and is classified as readily biodegradable based on a test with non-adapted, activated sludge under aerobic conditions. No tests are available that simulate the biodegradation of VAM in surface waters. In a recent study it was demonstrated that VAM is biotransformed in samples of soil sludge and sewage under aerobic and anaerobic conditions. Four yeasts and 13 bacteria feeding aerobically on VAM were isolated. Rates of transformation were higher under aerobic conditions, but anaerobic and aerobic degradation pathways both yielded the same products, i.e. acetaldehyde as an intermediate and acetic acid as a final product.

There is evidence that some soil organisms are also capable of decomposing polymers of vinyl acetate. It should be noted, however, that de-polymerisation is assumed to be the limiting step. Further biodegradation is rapid so that relevant VAM concentrations in environmental compartments are not to be expected.

VAM has only a low potential to adsorb to soils or sediments. Relevant transfer from the aqueous to the atmospheric compartment is expected. This transfer is mainly caused by volatilisation and air stripping during treatment of waste water, and to a lower degree by volatilisation from surface waters. The transfer to the atmosphere is to some extent counterbalanced by the high water solubility of the compound. Based on the Henry's law constant, VAM can be regarded as a moderately volatile compound.

Concerning the distribution of VAM between various environmental compartments it is expected that the major environmental compartment is air (91.5%), with a smaller proportion entering the aqueous compartment (8.4%) and just negligible quantities being predicted for other compartments. The fraction of VAM degraded in a municipal standard STP was estimated to be 78.2%, whereas 11.6% are expected to be directed to air, 10.0% to water and 0.2% to sludge.

VAM is not expected to bioconcentrate in terrestrial or aquatic organisms, nor to biomagnify in food chains, nor to geoaccumulate.

Environmental concentrations

Predicted Environmental Concentrations (PECs) are calculated for the local environments of the production and processing sites using all site specific information available. Data gaps are filled with the default values proposed in the Technical Guidance Document (TGD). The resulting water concentrations are in the range of 0 (no emission to waste water) to 1.03E+01 µg/l, air emissions in the range of 0 to 2.88E+02 µg/m³. However, in several cases it could not be clarified whether (co)polymerisation or compounding of already polymerised material or both was conducted at the sites.

As the difference between nominal production volume and verified processing capacities is rather high, a generic worst case scenario is included in the risk assessment to estimate the fraction of release at the local main source. A local water concentration of 8.12 µg/l and a local air concentration of 45µg/m³ is derived.

VAM may enter the terrestrial compartment mainly by aerial deposition and to a small extent by spreading of contaminated sewage sludge on soils. It is anticipated that VAM is relatively mobile in soil. Soil concentrations were estimated for the sites having the highest deposition rates (local soil concentrations of 9.95E-5 to 1.40E-3 mg/kg) and for the generic scenario (0.014 mg/kg).

Finished (co)polymers contain various concentrations of VAM residuals. Owing to the high volatility of VAM, it is anticipated that these residuals are exhaustively released during further life-cycle stages down the supply chain such as compounding into ready-to-use products. Further diffusive releases from end-use products during service lifetime are expected to be low. Nevertheless, a contribution of these products to regional background concentrations was considered.

Regional and continental environmental concentrations were derived taking into account releases of point sources and diffuse releases from products:

Continental PECs		**Regional PECs**	
$PECcont_{surfacewater}$	9.22E-07 mg l^{-1}	$PECreg_{surfacewater}$	8.33E-06 mg l^{-1}
$PECcont_{air}$	1.87E-06 mg m^{-3}	$PECreg_{air}$	9.67E-06 mg m^{-3}
$PECcont_{agr.soil}$	1.10E-07 mg kg_{wwt}^{-1}	$PECreg_{agr.soil}$	9.05E-07 mg kg_{wwt}^{-1}
$PECcont_{agr.soil,porew}$	2.02E-07 mg l^{-1}	$PECreg_{agr.soil,porew}$	1.66E-06 mg l^{-1}
$PECcont_{nat.soil}$	4.64E-08 mg kg_{wwt}^{-1}	$PECreg_{nat.soil}$	2.40E-07 mg kg_{wwt}^{-1}

3.2 EFFECTS ASSESSMENT

Aquatic compartment (incl. sediment)

For fish a chronic toxicity study on the early life-stages of fathead minnow is available. VAM was examined under flow-through conditions over a test period of 34 d and test concentrations were measured. The NOEC was determined to be 0.55 mg/l.

For invertebrates only acute test data are available. The only test which is considered to be valid has been conducted with *Daphnia magna* (semi-static, sealed test vessels, measured concentrations) and the 48 h EC50 (immobilisation) is 12.6 mg/l.

Similarly for algae there is only one valid test available with measured test concentrations (static conditions, sealed test vessels). The relevant endpoint is a 72 h NOEC (growth inhibition) of 5.96 mg/l.

As long-term NOECs from species representing two trophic levels are available, an assessment factor of 50 is used to derive the predicted no effect concentration (PNEC) from the long-term NOEC for fish.

$PNEC_{aqua}$ = 0.011 mg/l

The PNEC for sediments is calculated using the equilibrium partitioning method.

$PNEC_{sed}$ = 1.27 E-02 mg/kg

The toxicity of VAM to 2 different microorganisms was examined using cell multiplication inhibition tests. A 16 h EC3 of 6 mg/l was determined for *P. putida*. Based on this value and with an assessment factor of 10 the PNEC for sewage treatment plants is derived.

$PNEC_{STP}$ = 0.6 mg/l

Terrestrial compartment

No terrestrial effect data based on standard soil test organisms are available. Results from fumigation tests with fruit flies and molluscs are available, but according to the TGD can not be used for the derivation of the PNEC. Instead, the equilibrium partition method has to be used.

$PNEC_{soil}$ = 6.02E-03 mg/kg

Atmosphere

Test results are available from fumigation studies with fruit flies and molluscs and from inhalation studies with mammals. No experimental data on toxicity of VAM to terrestrial plants is available, so no $PNEC_{air}$ can be calculated.

VAM contributes only very little to global warming and acidification of surface waters. With regard to tropospheric ozone it can not be excluded that for specific meteorologic conditions and intensive solar irradiation the contribution to ozone peaks may be substantial in the immediate vicinity of emission sources.

3.3 RISK CHARACTERISATION

Aquatic compartment (incl. sediment)

Potential risks for sewage treatment plants are evaluated for all production, processing and manufacturing sites, including a generic scenario. No risks have been identified.

For surface waters site specific, generic and regional risk ratios have been calculated. All risk ratios are below one. However, at some processing sites risk ratios as high as 0.87 and 0.94 are calculated. The risk ratio for the generic processing scenario is 0.74.

A significant transfer of VAM into the sediment-phase is not expected due to the low adsorptive properties of VAM and its low affinity to organic matter. In addition VAM is hydrolytically and biologically degraded in sediments, so no unacceptable risks for sediments are expected.

Terrestrial compartment

It is expected that the main pathway of VAM immission into soil is aerial deposition after local releases to air from point source. Only 0.2% of the VAM load entering a STP is expected to adsorb to sludge, and most companies producing or processing ‘VAM reported either incineration or landfill of STP sludge.

As a worst case approach, soil concentrations were estimated for the two facilities with highest aerial deposition rates. Both facilities do not operate a STP so that sludge application is not included in the estimate. Furthermore, soil concentrations were calculated for several sites that had relatively high aerial deposition rates and reported sludge application on agricultural soils. All risk ratios for known production and processing sites of VAM are below one.

However, the PEC/PNEC ratio calculated in the generic scenario for unknown sites is 2.33, so a risk for the terrestrial compartment can not be excluded. The highest PEC/PNEC ratio calculated with site specific data (0.86) is not very far from the PEC/PNEC ratio calculated for the generic processing scenario, and there was also a risk at one of the production sites (which has been eliminated during the time of the preparation of the RAR). Consequently, it is not completely implausible that unknown processing sites pose a risk to the terrestrial environment. Risk reduction measures have to be considered at sites exceeding a processing capacity of 20,000 t/a. Sites already applying advanced techniques would not require further consideration of risk reduction measures.

Atmosphere

Due to the high volatility of VAM it is expected that the main compartment for environmental exposure is air. VAM breaks down rapidly in the atmosphere, hence transport from points of release over long distances can be excluded.

Besides photooxidation, wet deposition of VAM and its breakdown products is expected to be an important physical removal process from the atmosphere. Concurrently, cloud droplets further contribute to hydrolytic degradation of VAM in moist air. The reaction products show some acidification potential, but it is concluded that the specific contribution of VAM degradation products to acidification of surface waters will not be of any relevance as compared with other substances. From its high vapour pressure and low K_{ow} value it is concluded that either adsorption to airborne particles and aerosols is of relevance. In addition

there is no indication that VAM significantly adds to adverse effects on other parameters of atmospheric quality like global warming or ozone depletion.

At air concentrations of approximately 2 g/m^3 significant biotic effects were observed. However, the data basis is far too scarce to derive a PNEC from this test result. As the highest calculated local concentration of approx. 0.3 $\mu g/m^3$ is several orders of magnitude lower, further tests on this endpoint seem not to be of high priority.

It is concluded that an unacceptable risk for the environment via the atmosphere is not expected from vinyl acetate.

Secondary poisoning

As there is no indication for vinyl acetate to be a potentially bioaccumulative substance, it was abstained from assessing effects for secondary poisoning.

PBT Assessment

VAM does not meet the PBT/VPVB criteria.

Marine Assessment

There is no indication that VAM persists or accumulates in the environment. However, it is known that two production sites and one processing site discharge to the marine or estuarine environment. PEClocal for these sites are based on site-specific data in combination with default values from the TGD. As a first approach, the marine regional background concentration was derived from the fresh water regional background concentration by division by 10. The $PNEC_{marine}$ was derived by dividing the $PNEC_{aqua}$ by 10. Based on these values, PEC/PNEC ratios below one are derived for all sites.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY0

4.1.1 Exposure assessment

Occupational exposure

Vinyl acetate is a monomer, solely used to manufacture vinyl acetate (co)polymers. Hence it is concluded that the entire production volume of vinyl acetate monomer is used up for the manufacture of various (co)polymers, mainly polyvinyl acetate. Apart from manufacture of homopolymers the monomer is combined with other monomers like ethylene, vinyl chloride and acrylic acid esters to form various types of co-polymers. Polymers manufactured from vinyl acetate monomer are used in a broad spectrum of products, including water-based paints, printing inks, lacquer, ceramic, adhesives for packaging and construction, paper finishing, and protective colloids for various materials.

Detailed information on the production volumes and the use is given in chapter 2.

Vinyl acetate occurs as residual monomer in homo- and copolymers based on vinyl acetate and in products / formulations based on these polymers. The content of residual vinyl acetate monomer in homo- and copolymers depends on the product and the field of application (< 2 - 3000 ppm).

The following national occupational exposure limits (OEL) are given (2008):

Finland, Austria, Greece, Belgium, Spain	36 mg/m^3 (10 ml/m^3)
USA: ACGIH, Italy, Portugal	35 mg/m^3 (10 ml/m^3)
Ireland, Denmark, France, Norway	30 mg/m^3 (10 ml/m^3)
Sweden, Germany, The Netherlands	18 mg/m^3 (5 ml/m^3)

Relevant occupational exposure scenarios are to be expected in the following areas:

- Production of vinyl acetate and polymerisation in the chemical industry (scenario 1)
- Manufacturing of formulations and products (scenario 2)
- Use of formulations and products containing residual vinyl acetate monomer (scenario 3)

The exposure assessment is based on measured data and estimations according to the EASE model (Estimation and Assessment of Substance Exposure). The exposure levels should be regarded as reasonable worst case estimates representing the highly exposed workers.

Based on the available information, the exposure assessment reveals that handling the monomer substance in the areas of production and polymerisation, the formulation of adhesives as well as the use of formulations, especially of adhesives, are the main source for occupational exposure. Direct uses of the substance other than polymerisation are not known. Applications of the manifold products containing vinyl acetate in traces as residual monomer, e.g. adhesives, coating materials and paints, are regarded to be of minor relevance.

For the large-scale chemical industry, it is assumed that the production and polymerisation of vinyl acetate is mainly performed in closed systems with high levels of protection. Exposure

occurs if the closed systems are breached for certain activities e. g. filling, cleaning and sampling in the area of manufacturing and polymerising of vinyl acetate monomer (scenario 1). Dermal exposure is assessed using the EASE model. In addition, the high vapour pressure of vinyl acetate is taken into account as an exposure reducing effect.

According to information provided by industry, there is normally no use of vinyl acetate monomer in formulating facilities and exposure is limited to the use of vinyl acetate (co)polymers containing < 2 – 3000 ppm residual monomer. However, some adhesive producing facilities use vinyl acetate monomer for (co)polymerisation and perform the formulation subsequently. Therefore, this exposure scenario comprises the polymerisation step (use of vinyl acetate monomer) and the formulation step (residual vinyl acetate in (co)polymers). Generally, in formulating facilities different levels of protection are realised. In part, processes like filling and mixing are performed in open systems. Measurement results are available from formulating adhesives only. At present it is assumed, that the high levels relate to the use of vinyl acetate monomer (polymerisation step). If no monomer is handled and a company uses only vinyl acetate (co)polymers (formulation step), exposure is expected to be considerably lower.

The widespread industrial and skilled-trade applications of polymeric dispersions and solid resins containing residual vinyl acetate monomer (up to 3000 ppm) comprise uses in paints, lacquers, adhesives, plasters and coating materials. In scenario 3 a worst case situation is described assuming 3000 ppm residual monomer and daily exposure during the whole shift.

Table 4.1: Summary of exposure data

Exposure scenario	Duration and frequency of activities relevant for exposure	Inhalation exposure Shift average [mg/m^3]	Dermal exposure Shift average [mg/p/day]
1) Production and further polymerisation in the chemical industry	8 hour, daily	3.0 (workplace measurement, 95th percentile)	42 [1)] (EASE, with gloves)
2) Manufacturing of formulations and products (e.g. adhesive production)	8 hour, daily (assumed)	14.6 (workplace measurement, 90th percentile)	420 [1)] (polymerisation step EASE, without gloves)
			1.3 [2)] (formulation step EASE, without gloves)
3) Use of formulations and products containing residual vinyl acetate monomer (3000 ppm)	8 hour, daily (assumed)	2.6 (worst case conditions)	12.6 [2)] (EASE, without gloves)

(1) The EASE estimate is largely reduced because of the short duration time of dermal exposure. The retention time of pure vinyl acetate is calculated to 1 second for 0.1 mg/cm² and to 10 seconds for 1 mg/cm² (order of magnitude) independent on the use of gloves (non-occlusive exposure).

(2) Worst case estimation assuming 3000 ppm residual monomer. Due to the high vapour pressure of the substance shortened retention times on the skin are to be expected leading to considerable lower dermal exposure levels than estimated with the EASE model. For vinyl acetate in mixture the retention time cannot be calculated because of the complex composition of the mixtures and their specific drying behaviour.

Consumer exposure

According to the Swedish product register, products containing vinyl acetate are used by consumers in Sweden. Such products are e.g. moisture barrier paints and other paints and lacquers/varnishes on a solvent basis, adhesives, glues, dispersion adhesives, hotmelt adhesives and sealing compounds. The consumer products are offered in wholesale and retail trade, e.g. in repair shops for motor vehicles and motorcycles as well as for personal and household goods (as per February 1995).

In the Norwegian product register, 15 products for use in the consumer field have been listed in which vinyl acetate is used as a component of paints for the exterior and interior application to houses (as per 16 December 1994). No information is available for the amount of vinyl acetate in the formulations.

In the Federal Republic of Germany, polyvinyl acetate is known to be used e.g. as a component of adhesives (vinyl acetate polymer content up to 36%), car polishing products (primers, polyvinyl acetate copolymer content up to 1.5%), hair care products (hair setting lotions, vinyl acetate copolymer content up to 3%, hair care products) and in plastics for toys and those coming into contact with foods. These products contain traces of vinyl acetate as a residual monomer; in adhesives (e.g. film and surface adhesives), the residual monomer content is 0.1 - 0.2% (voluntary reporting by the manufacturers/distributors etc. to the BgVV.

In case reports from the Swiss Toxicological Information Centre, polyvinyl acetate is stated as a component of paints and lacquers/varnishes (binding materials) for households. According to the data provided by the manufacturers, the concentration of polyvinyl acetate is up to 13%, and that of vinyl acetate as a residual monomer up to a maximum of 0.3% in the (co)polymer. In water-based paints residual vinyl acetate monomer hydrolyses rapidly.

According to information provided by the industry, poly vinyl acetate is used in printing inks. The maximum polymer concentration is 60%, the maximum concentration of the residual monomer is 0.2%; this results in a maximum content of vinyl acetate monomer of 0.12%.

Following the exposure assessment there is no direct exposure of the consumer to vinyl acetate besides of the release of monomers from polymers. Overall exposure of consumers to vinyl acetate results mainly from inhalation due to emissions from carpets, paints and adhesives. However, there is a lack of sufficient data on other uses. For comparison with acute effects, the estimate for short-term exposure from carpets will be used (concentrations of 1 mg/m³). With regard to chronic effects, the concentration of 0.036 mg/m³ for long-term exposure will be used resulting in an exposure of 9.2 µg/kg bw/d for men, 4.6 µg/kg bw/d for women, and 18 µg/kg bw/d for children. For the risk characterisation a value of about 10 µg/kg bw/d for adults will be used.

The dermal exposure to vinyl acetate is estimated to be about 1 µg/kg bw/d.

The sum of all types of exposure resulting from residual monomeric vinyl acetate (reasonable worst case) is estimated to be in the range of 5 to about 20 µg/kg bw/d.

Humans exposed via the environment

According to Appendix VII of chapter 2 of the TGD, the indirect exposure to humans via the environment, i.e. through food, drinking water and air is estimated.

As a worst case scenario, the maximum intake due to exposure in the vicinity of a vinyl acetate production facility is calculated (site 26). This is compared to an average intake due to exposure via the regional background concentration.

The resulting total daily dose is: $DOSE_{tot\_local}$ = 36 µg / kg $_{bw}$ d

$DOSE_{tot\_regional}$ = 2.47 E-03 µg / kg $_{bw}$ d

The calculated total doses comprise the following routes:

Route	**Percent of total dose**	
	local	**regional**
Drinking water	1.26	9.64
Fish	2.97E-05	0.44
Stem	0.36	0.33
Root	0.24	0.37
Meat	2.04E-04	2.41E-04
Milk	3.80E-03	4.50E-03
Air	98.13	89.22

The main route of indirect exposure of both scenarios is the intake via inhalation of air.

Combined exposure

[click here to insert text]

4.1.2 Effects assessment

Toxicokinetics, metabolism and distribution

Following inhalation and oral exposure of rats vinyl acetate is rapidly and effectively hydrolysed by carboxylesterases leading to the formation of acetic acid and acetaldehyde which is further converted into acetic acid in the presence of aldehyde dehydrogenases. Further information on acetaldehyde and acetic acid can be obtained from separate reports (e.g. reports prepared by the German MAK Commission).

The in vivo uptake of vinyl acetate was measured in the isolated upper respiratory tract of rats (anaesthetised rat, unidirectional flow, and 1 h-exposure). Disappearance of vinyl acetate from the airstream was highest at the lowest exposure concentrations. Greater than 94% extraction was observed at vinyl acetate exposure concentrations of 76 ppm or below. With increasing exposure concentration (76 to 550 ppm), extraction decreased progressively to about 40% and remained at this level up to concentration of approximately 2000 ppm. The impact on blood-flow extraction on vinyl acetate deposition has been calculated by simulating vinyl acetate exposure in the absence of carboxylesterase activity. It could be demonstrated, that blood flow extraction accounts for less than 15 % of total vinyl acetate deposition. Hence, 15 % inhalative uptake can be taken as a worst case scenario for risk characterisation of systemic effects. However, it should be kept in mind, that vinyl acetate can be degraded in the blood with half lives between < 1 min and 4.1 min.

After oral administration of 297 mg/kg/bw ^{14}C vinyl acetate, 63 % of the applied radioactivity was excreted as metabolites in exhaled air, urine and faeces. Based on the fact that vinyl acetate can be metabolized in the upper GI tract epithelium it can be assumed, that a considerable extent of metabolism takes place presystemically which is supported by an oral PBPK model (see below). This model led to the conclusion, that clearance of vinyl acetate and its metabolites into the systemic circulation would be negligible. Hence, 63 % absorption would represent an overestimation of systemically available amounts of vinyl acetate. However, the PBPK model developed for oral vinyl acetate exposure did not include systemic components and furthermore, the model was developed in the absence of valid data for carboxylesterases in animal and human tissues. Based on the fact, that carboxylesterases in the GI tract are lower compared to carboxylesterase activities in nasal tissues, 50 % absorption can be assumed as a worst case for systemically available amounts of vinyl acetate after oral uptake. However, no clear assumptions can be made for systemically available metabolites of vinyl acetate (acetaldehyde, acetic acid).

There are no valid quantitative data on the systemic bioavailability of vinyl acetate and its metabolites following dermal exposure. However, based on an acute dermal study in rabbits and based on the fact that carboxylesterase activities are lower in skin compared to nose or oral cavity, it can be assumed that systemic bioavailablility of vinyl acetate and/or vinyl acetate-derived metabolites is higher after dermal exposure when compared to oral or inhalative exposure. Therefore 90 % dermal absorption should be taken forward to the risk characterisation.

Local metabolism was studied in human and rat nasal respiratory and olfactory tissue with whole turbinates in vitro. The studies indicated species differences of nasal respiratory carboxylesterase activities between rats and humans. The differences varied depending on the mode of data presentation (activity per specimen/activity per epithelial cell volume/activity

scaled to whole nose). Therefore, no clear conclusions on the magnitude of species differences of nasal respiratory carboxylesterase activities can be drawn from these investigations. Rat aldehyde dehydrogenase activity in respiratory epithelium was about twice that of humans. Activities of the rat olfactory enzymes (carboxylesterase and aldehyde dehydrogenase) were about equivalent to those of humans. The K_m values for both enzymes are not different between the two species. Aldehyde dehydrogenase activities determined in whole nasal tissue homogenates from mouse, rat, hamster and guinea pig showed significantly different ratios V_{max}/K_m for the various species indicating the existence of species differences.

Vinyl acetate hydrolysis has been studied in vitro in the oral mucosal tissues from the oral cavity of rats and mice. The hydrolysis activity of the oral tissues is at least 100-fold lower than that of the nasal tissues.

A physiologically based pharmacokinetic model was developed which describes the deposition of vinyl acetate in the nasal cavity of the rat. This model predicts steady state concentrations of the metabolite acetic acid after continuing 6 h-exposure in respiratory tissue which are approximately 13 times greater and in olfactory tissue which are approximately 2 times greater than those of acetaldehyde, the second metabolite. As the concentration of acids is indicative for the concentration of protons the model predicts the greatest reduction in intracellular pH_i for respiratory mucosa. Hence, pH effects should be more pronounced in this tissue as compared to other tissues. This physiologically based toxicokinetic/toxicodynamic model for rat was modified for the olfactory epithelium of the both human and rat nasal cavity. The change in intracellular pH is predicted to be slightly greater for human olfactory epithelium, than that of rats. To provide validation data for this model, controlled human exposures at exposure levels of 1, 5 and 10 ppm to inhaled vinyl acetate were conducted. Air was sampled by a probe inserted into the nasopharyngeal cavity of five volunteers at bidirectional breathing through the nose. Data from ion trap mass spectrometry measurements of labelled vinyl acetate and acetaldehyde were compared with data from the human nasal model simulation. For the vinyl acetate data a good fit was demonstrated ($r = 0.9$). Acetaldehyde data are fitted with a somewhat lower precision. The results show that the human nasal model predicts the experimental observations with regard to vinyl acetate concentrations and the acetaldehyde washout in the airstream of human nasopharyngeal cavity in a concentration range from 1 to 10 ppm. However, uncertainties of the model consist in the enzyme kinetic data used to establish the model. Therefore, data on PK and PD outcome derived from the model should be taken with caution.

A similar PBPK model with a pharmacodynamic submodel for the upper GI tract of mouse, rat and man was developed to estimate oral vinyl acetate uptake, metabolism and the reduction in the intracellular pH. The model was used to estimate steady state concentrations (24 h exposure) of acetic acid, acetaldehyde and intracellular proton concentration in the epithelial cell layer for a range of vinyl acetate exposure from 400 to 10000 ppm in drinking water. Details of model simulations are given for mouse. The intracellular pH reduction from the resting-phase proton concentration is about 0.4 and 0.7 pH units at a vinyl acetate exposure of 400 and 2000 ppm, respectively. Due to missing human data (carboxylesterase activity and tissue thickness) the exact variability in the internal dose-metric in humans cannot be accurately predicted from the PBPK model.

Acute toxicity

Human data on the acute toxicity of vinyl acetate are not available. In tests with rats LD_{50} values were in two studies 3470 mg/kg and 3500 mg/kg, respectively. A dermal LD_{50} value of 7440 mg/kg was determined from a range finding study with rabbits. Thus, vinyl acetate needs no labelling according to EU criteria with respect to acute oral and acute dermal toxicity. Inhalation toxicity testing, however, resulted in LC_{50} values of 15.8 mg/l/4 hours and 14.1 mg/l/4 hours in rats; thus requiring classification as harmful and labelling with „R 20, harmful by inhalation".

Irritation

Except a general notice from occupational use no substantiated human data on irritation/corrosion caused by vinyl acetate are available.

Due to the only valid tests (RCC, 2003a and c) mild irritative effects on the skin and eyes of rabbits were observed that do not warrant classification. Earlier studies of limited reliability indicated pronounced irritation or corrosion of skin after extended exposure periods.

Acute inhalation tests with rats demonstrated severe irritation in the respiratory tract of the animals. Thus, vinyl acetate should be labelled „R 37 Irritating to respiratory system according to the Annex I rules. In September 2007 the TC C&L agreed on R37.

Corrosivity

Due to data on irritation there is no evidence that the substance is corrosive.

Sensitisation

No cases of skin sensitization from the handling of vinyl acetate in the workplace have been reported in the last years. However, the data obtained for humans at the workplace are of limited value for assessing skin sensitising potential of vinyl acetate. There are no data on negative patch tests to substantiate the conclusion that the substance has no skin sensitising potential. The absence of positive findings and the absence of adequate data do not allow the conclusion that vinyl acetate has no skin sensitising potential.

Results from an animal skin sensitization study (Buehler Test) showed a moderate skin sensitising potential of vinyl acetate (commercial grade). With the use of the Local Lymph Nodes Assay (LLNA) no positive stimulation responses were detected at concentrations of 5% - 100%. Increased ear thickness after treatment with concentrations >5% support the skin irritative properties seen after prolonged dermal exposure. However, the results obtained with this LLNA may not fully reflect the potential of concentrations >10%, since higher concentrations of vinyl acetate show increasing volatility, due to decreased proportions of acetone/olive oil. As a result, samples applied to the skin of the ear may have been quickly evaporated. SI values support this assumption, since a constant decrease was obtained for concentrations > 10%.

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

No direct information is available from studies in humans on respiratory sensitization. In view of the widespread use, the absence of any reports suggests that vinyl acetate may not be a respiratory sensitiser.

Repeated dose toxicity

The major toxic effects after prolonged inhalation of vinyl acetate in experimental animals were lesions of the surface epithelium of the upper and lower respiratory tract. Degeneration, regenerative/reparative processes, inflammation, hyperplasia and metaplasia were noted in the nasal mucosa. They were most pronounced in the olfactory epithelium occurring at 200 ppm in rats and mice during and at the end of a 2-year exposure period. Lesions of the respiratory epithelium were seen in mice exposed to 600 ppm during and at the end of 2 years, whereas rats demonstrated lesions at this site only at a high concentration of 1000 ppm (4 week study). Characteristic alterations of the larynx and trachea of mice in the 600 ppm groups were hyperplasia and metaplasia along with desquamation and fibrosis in the trachea. Similar changes of the bronchial and bronchiolar airways were reported for rats and mice at this concentration at the end of the 2-year exposure period. In addition, clinical signs of non-specific toxicity and irritation were evident, but no relevant toxic effect on any organ could be identified. From the 2-year studies, the NOAEC for local toxic effect on the respiratory tract was 50 ppm (178.5 mg/m³) in rats and mice. Based on growth retardation in rats of the 600 ppm groups and mice of the 200 ppm groups, the NOAEC for systemic toxicity was considered to be at 50 ppm (mice 178.5 mg/m^3).

No specific organ toxicity was recorded after repeated oral administration of vinyl acetate with drinking water to rats and mice. A subchronic 13-week study revealed a slight (non-significant) reduction of food consumption and growth retardation in male rats at 5000 ppm (684 mg/kg bw/d). As NOAEL for systemic effects the value of 684 mg/kg bw/d (male rat) will be used in the risk characterisation.

As lesions of the respiratory tract epithelia occurred at concentrations above the critical concentration values according to the Annex VI criteria, there is actually no need for classification and labelling with respect to repeated dose toxicity.

Mutagenicity

Vinyl acetate is negative in bacterial mutagenicity tests.

In mammalian cell cultures various cytogenetic effects were induced in the absence of S-9 mix (chromosomal aberrations, micronuclei, SCE) and in the presence of S-9 mix (SCE; chromosomal aberrations and micronuclei not analysed with S-9 mix). The lowest positive

concentrations ranged from 0.1 to 0.2 mmol/l. A positive mouse lymphoma assay is in line with these results, but it cannot be deduced whether the positive effect is due to chromosomal or to gene mutations (no colony sizing). Mammalian cell culture investigations on DNA strand breaks (DSB) and DNA protein crosslinks (DPX) were negative (DSB), or extremely high concentrations were needed for positive effects (DPX).

Very few reliable data are available on the in vivo mutagenicity of vinyl acetate. A weak induction of micronuclei in mouse bone marrow cells was clearly limited to intraperitoneal doses in the LD50 range (1000 and 2000 mg/kg bw). In rats no induction of micronuclei was observed in spermatids (screening assay with intraperitoneal doses up to 1000 mg/kg bw). Further tests on induction of micronuclei or chromosomal aberrations were of too low reliability.

Also in an SCE test with rats positive effects were weak and limited to high and probably highly toxic intraperitoneal doses (370 and 470 mg/kg bw). Such weak increases in SCE frequencies may well be induced by unspecific effects on the cell cycle.

No specific DNA binding was observed in rat livers after inhalation or oral administration.

Induction of sperm abnormalities in mice again was limited to doses in the toxic range. Furthermore, it is not specific for mutagens.

No clear conclusion can be drawn from a human study on the possible induction of chromosomal aberrations in workers exposed to vinyl acetate.

Genotoxicity data on vinyl acetate metabolites are in line with the hypothesis that vinyl acetate genotoxicity is mediated by acetaldehyde. The genotoxicity of acetaldehyde is possibly limited to an overloading of defence mechanisms.

Altogether, vinyl acetate has a mutagenic potential, which is preferentially expressed as clastogenesis. The data on in vivo genotoxicity are difficult to interpret, since their majority is of low reliability, or the effects are not specific to mutagenicity. The most important effect, a weak induction of micronuclei in mouse bone marrow, is limited to intraperitoneal doses of high toxicity. Therefore, it is unlikely that the genotoxic potential of vinyl acetate is expressed in germ cells in man. However, genotoxic effects locally in directly exposed tissues (site of first contact) cannot be excluded; the occurrence and strength of the effects will be dependent on the metabolic capacity of the directly exposed tissue.

No classification of vinyl acetate in terms of germ cell mutagenicity is proposed.

Carcinogenicity

In cancer studies, vinyl acetate inhalation induced an increased number of nasal tumors (mainly papillomas and squamous cell carcinomas) in various regions of the nasal mucosa of rats. The total incidence was significantly increased at a concentration of 600 ppm (2142 mg/m^3) but a single papilloma already developed at 200 ppm. No significant tumor response was seen in a mice cancer bioassay. Occasionally single squamous cell tumors occurred at other sites of the respiratory tract in rats and mice.

Oral cancer studies were also positive. Significantly increased incidences of benign and malignant squamous cell tumors in the oral cavity in rats and mice, in the esophagus and forestomach in mice were observed in 2-year drinking water studies at vinyl acetate concentration of 10000 ppm (dose ranges in rats 364-1062 mg/kg bw/d, in mice 800-2185 mg/kg bw/d). Similar results were found in another non-guideline conform cancer study on

two generations of mice treated orally with 5000 ppm vinyl acetate in the drinking water (780 mg/kg bw/d). Higher rates of tumors were noted in the oral cavity, tongue, esophagus, forestomach (squamous cell carcinoma at all sites) as well as in the glandular stomach.

Vinyl acetate is considered as a threshold carcinogen because it is thought that carcinogenic action affects the site of first contact only a high concentrations. Cytotoxicity was assumed as one underlying mode of carcinogenesis in the olfactory mucosa. The assumption was thought to be supported by consistent dose-response and time-response relationships between cytotoxic effect and tumor growth. No cytotoxicity as a prerequisite of tumor development was identified for the other tumor sites, the non-olfactory regions and the upper gastrointestinal tract. However, increases in cell proliferation combined with increased formation of DNA adducts were only seen a high concentrations of vinyl acetate. Both effects are considered to be mediated by acetaldehyde that accumulates intracellularly when the physiological balance of intracellular formation and detoxification is disrupted above a certain, albeit unknown concentration of acetaldehyde. Instead, the most sensitive effects, the cytotoxicity of the olfactory region for the inhalation route (NOAEC 50 ppm), and the tumors of the upper gastrointestinal tract for the oral route (LOAEL 400 ppm), are recommended for risk characterisation.

No adequate data from human experience are available. Based on the carcinogenic potential of vinyl acetate in two animal species and at the inhalative and oral route and the absence of reliable human data the substance might pose a cancer risk for humans. Carcinogenicity is thought to act via a secondary mechanism and the concern may only be relevant above threshold concentrations.

Toxicity for reproduction

Vinyl acetate has been investigated in rats for adverse effects on reproductive performance and fertility via the oral (drinking water) route of exposure and in mice for adverse effects on male reproductive organs via the i.p. exposure route. Vinyl acetate was shown to reduce testicular weight and to induce sperm abnormalities in mice, however at toxic dose levels inducing mortality and body weight loss. Vinyl acetate was further shown to have marginal influences on reproduction at oral exposure levels that lead to significantly reduced water intake (probably due to palatability) associated with significantly reduced body weight gain. The observed effects comprised reduced pup weights and slightly lower numbers of pregnancies. Distinct reproduction related adverse effects of vinyl acetate were not evidenced from a two generation study with rats for drinking water concentrations of up to and including 1000 ppm.

The developmental toxicity of vinyl acetate has been investigated in rats via oral (drinking water) and inhalation exposure routes during organogenesis. No embryo/fetotoxic or teratogenic effects were observed for the oral route of administration at drinking water concentrations of up to and including 5000 ppm. Fetotoxic effects, revealed during inhalation exposure, were confined to high dose levels only, where severe maternal toxicity was observed. However, vinyl acetate did not adversely affect both the dam and the conceptus at an inhaled concentration of up to and including 200 ppm.

A NOAEL/fertility of 1000 ppm (equivalent to dosages of about 100 mg/kg bw/day) was derived from a study with oral exposure, and a NOAEC/developmental toxicity of 200 ppm (equivalent to dosages of about 205 mg/kg bw/day) was derived from a study with inhalation exposure.

4.1.3 Risk characterisation

Workers

Introduction to occupational risk assessment

This occupational risk assessment is based upon the toxicological profile of vinyl acetate (chapter 4.1.2) and the occupational exposure assessment (chapter 4.1.1). The threshold levels identified in the hazard assessment are taken forward to this occupational risk assessment.

In table 4.2 the exposure levels of table 4.1 are summarised and the route-specific and total internal body burdens are identified. Risk assessment for combined exposure requires the calculation of a total internal body burden; to this end the derived route-specific percentages for absorption are used (15% for inhalation and 90% for dermal exposure).

Table 4.2: Occupational exposure levels and internal body burden of vinyl acetate

Exposure scenario		Inhalation (shift average)	Dermal contact (shift average)		Internal body burden of workers after repeated exposure		
					Inhalation[1]	Dermal[2]	Combined
		mg/m^3	mg/p/d	mg/kg/d	mg/kg/d		
1. Production and polymerisation in the chemical industry		3[3]	42[5]	0.6	0.064	0.54	0.60
2. Manufacturing of formulations and products	a) polymerisation step (vinyl acetate monomer)	14.6[3]	420[6]	6	0.31	5.4	5.71
	b) formulation step (vinyl acetate (co)polymer)		1.3[6]	0.02		0.018	0.33
3. Use of formulations and products containing residual vinyl acetate monomer		2.6[4]	12.6[6]	0.18	0.056	0.16	0.22

[1] based on the assumption of 15% inhalative absorption; breathing volume of 10 m^3 per shift
[2] based on the assumption of 90% systemic availability of vinyl acetate after dermal contact
[3] reasonable worst case
[4] worst case
[5] EASE (90 % protection by suitable gloves)
[6] EASE (without gloves)

MOS approach

The MOS approach for human risk characterisation is described in detail in the TGD (Human Health Risk Characterisation, Final Draft). The following chapter contains a short

introduction to the MOS approach used. The basic principle of the MOS approach is a comparison of scenario-specific MOS values (the relationship between the experimental NOAEL respectively the adjusted starting point and the exposure level) with a reference MOS (product of various assessment factors).

MOS calculation and the adequate starting point

Basically, MOS values are calculated as quotient of a relevant NOAEL from experimental animal testing or human studies and actual workplace exposure levels. In specific situations, the MOS approach requires a conversion of the original NOAEL into an adequate starting point or corrected NOAEL previously to MOS calculation in order to be directly comparable to the exposure assessment. If the route of application in animal or human studies is different from the actual occupational exposure, the dose units of the experimental data should be converted to the dose unit of the exposure data. Additionally, possible differences in bioavailability between routes, as well as possible differences in bioavailability between animals and humans should be accounted for the calculation of the corrected NOAEL. For vinyl acetate 15% absorption after inhalation, 50% after oral exposure, and 90% absorption after dermal contact is assumed (see chapter 4.1.2).

For occupational risk assessment, the corrected NOAEC for inhalation accounts for the difference of the standard respiratory volume (6.7 m^3) and the respiratory volume for light activity (10 m^3). MOS values are calculated for different routes of exposure and for different toxicological endpoints. The routes of exposure specifically considered in occupational risk assessment are exposure by inhalation and dermal contact. In addition, for risk assessment of combined exposure (exposure by inhalation and dermal contact) an adequate NOAEL is derived from external NOAELs and specific information on route-specific absorption. For MOS calculation, the adjusted internal starting point is divided by the internal body burden. Depending on route-specific exposure and absorption, inhalation exposure and/or dermal exposure may contribute to the internal body burden. With respect to the possible outcome of an assessment for combined risks, interest focuses on scenarios with conclusion ii at both exposure routes. Based on theoretical considerations, combined exposure will not increase the most critical route-specific risk component more than twice.

Reference MOS

The MOS values calculated have to be compared with a reference MOS. The reference MOS is an overall assessment factor, which is obtained by multiplication of individual assessment factors. The Technical Guidance Document emphasises several aspects which are involved in the extrapolation of experimental data to the human situation. For these assessment factors, default values are recommended. It is important to point out that any relevant substance-specific data and information may overrule the defined default values.

Interspecies extrapolation on the one hand is based on allometric scaling (factor 4 for rats, factor 7 for mice, and factor 2.4 for rabbits). For remaining interspecies differences the TGD proposes an additional factor of 2.5. Interspecies extrapolation conceptually might be considered to consist of a toxicokinetic and toxicodynamic phase. As to vinyl acetate PBPK models essentially describe the relationship between airborne concentration of vinyl acetate and intracellular acetaldehyde concentration. However, uncertainties of the model consist in the enzyme kinetic data used to establish the model. Therefore, data on toxicokinetic and toxicodynamic outcome derived from the model should be taken with caution. For

occupational risk characterisation an interspecies factor of 2.5 is proposed (abutted at the default value for the remaining uncertainties of interspecies differences). For workers, an adjustment factor for intraspecies differences of 5 is recommended. Based on an evaluation of empirical data by Schneider et al. (2004) it is anticipated that a factor of 5 will be sufficient to protect the major part of the worker population (about 95%). In the case of vinyl acetate PBPK results are available (see chapter 4.1.2 and 4.1.3.2), which suggest that the toxicodynamic portion of the default intraspecies factor (10 for the whole population, 5 for workers) remains as overall intraspecies factor since the toxicokinetic part (4) is not applied (no systemic metabolism as it is virtually impossible that vinyl acetate will reach the systemic circulation). The remaining uncertainties are covered by application of a reduced adjustment factor for workers in the range of 1.25 and 2.5.

For chemical substances it is usually expected that the experimental NOAEL will decrease with increasing duration of application. Furthermore, other and more serious adverse effects may appear with prolonged exposure duration. For duration adjustment, a default factor of 6 is proposed for extrapolation from a subacute to chronic exposure. The duration adjustment factor is lower (a factor of 2) for the transition from subchronic experimental exposure to chronic exposure. Since chronic studies are available for vinyl acetate, a specific factor for duration adjustment of repeated dose toxicity is not necessary.

The MOS values for different toxicological endpoints and different exposure scenarios are compared with the substance- and endpoint-specific reference MOS. MOS values clearly above the reference MOS do not lead to concern, whereas MOS values that are clearly below the reference MOS are cause for concern. There may be various risk-related aspects which are not covered by default assessment factors. These additional qualitative aspects should be carefully considered when performing a risk assessment and should have adequate influence on finding of conclusions.

Critical Exposure Levels

In a parallel procedure, which gives identical but more direct results, the adjusted toxicological starting point is directly divided by the reference MOS. As a result, an exposure level (in mg/m³ or mg/kg/d) is identified, which may serve as a direct trigger for decisions when compared with the occupational exposure levels. In the context of this risk assessment report this trigger value is called “critical exposure level”. Concern will be expressed for scenarios with occupational exposure levels higher than the relevant “critical exposure level”.

Acute Toxicity

Local effects ***see irritation, no further information available***

systemic effects

Inhalation and dermal Exposure

conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already

Acute toxicity data for humans are not available.

Comparing the LC_{50}-value of ca. 15,000 mg/m^3 for rats and the concentration of 7,000 mg/m^3 without lethality with the highest inhalation exposure concentration of 15 mg/m^3 (scenario 2, reasonable worst case) and the highest short-term exposure of 47 mg/m^3 (scenario 2) a relevant risk concerning acute toxicity is not expected under normal workplace conditions.

Comparing the LD_{50} of 7,440 mg/kg for rabbits and the dose of 3,720 mg/kg (no mortalities, but effects in different organs) with the highest dermal exposure of 6 mg/kg (scenario 2a, use of vinyl acetate monomer) a relevant risk concerning acute toxicity is not expected under normal workplace conditions.

Irritation/Corrosivity

conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already

Skin, Eye

Due to the only valid tests mild irritation of the skin and the eyes of rabbits were observed that do not warrant classification. No concern for dermal or eye irritation at the workplace is expressed.

Respiratory tract

According to chapter 4.1.2 vinyl acetate has proven to cause severe irritation in the respiratory tract of rats. From these animal data a value of 200 ppm (corresponding to 710 mg/m^3) was derived that will be used as NOAEC, concerning local effects after short term inhalative exposure.

A MOS calculation would result in a value of about 79 mg/m^3 (inhalation starting point of 476 mg/m³ with the NOAEC of 710 mg/m^3 multiplied by 6.7/10 (activity-driven differences of respiratory volumes in workers) divided by a reference MOS of about 3 – 6 (intraspecies differences factor 1.25 – 2.5 and interspecies factor of 2.5). Comparing the critical exposure level of 79 mg/m^3 with the highest exposure of 14.6 mg/m^3 (scenario 2) a relevant risk concerning irritation after inhalation is not expected under normal workplace conditions.

Skin and respiratory sensitisation

conclusion (ii) There is at present no need for further information and/or testing and no need for for risk reduction measures beyond those which are being applied already

No cases of skin or respiratory sensitization from the handling of vinyl acetate in the workplace have been reported in the last years. Given the results of an animal skin

sensitization study and a Local Lymph Node Assay classification and labelling with R 43 is not warranted. In summary concern is not expressed.

Repeated dose toxicity

Local effects

Inhalation

conclusion (iii) There is a need for limiting the risk; risk reduction measures which are already being applied shall be taken into account

Based on experimental animal data the NOAEC for local effects on the respiratory tract was 50 ppm (180 mg/m^3) which is taken as starting point for the risk assessment of local effects after repeated exposure. This experimental NOAEC of 180 mg/m^3 is (1) adapted by a factor of 6/8 to account for differences between the experimental inhalation duration of 6 hours per day and the average working day of 8 hours per day, and (2) is multiplied by a factor of 6.7/10 for activity-driven differences of respiratory volumes in workers. This results in an adjusted inhalation starting point of 90 mg/m^3 (180 • 6/8 • 6.7/10).

The reference MOS accounts with the intraspecies differences with a factor of 1.25 – 2.5. The interspecies differences deal with a factor of 2.5 (the factor for allometric scaling is already implicitly applied). Duration adjustment is not necessary, because a long term study is available. This would result in a reference MOS of about 3 – 6 (5 • 1.25 – 2.5) and a critical exposure level of 15 to 30 mg/m^3 depending on how big the factor for intraspecies differences is dealt with. Comparing this range for a critical exposure level of vinyl acetate with the OEL of 17.6 mg/m^3 (5 ppm) which was set by the Scientific Committee on Occupational Exposure Limits, the value is very close at the lower value of 15 mg/m^3. For pragmatic reasons the occupational exposure value of 17.6 mg/m^3 (5 ppm), which was set by SCOEL (2005) is taken forward to this risk assessment. The SCOEL value corresponds to a reference MOS value of 5.1.

The highest shift average value for inhalation is reported as 14.6 mg/m^3 for manufacturing of formulations and products of vinyl acetate in scenario 2. Compared with the OEL of 17.6 mg/m^3 the scenario reaches borderline. Conclusion iii is drawn for this borderline scenario since there is the uncertainty concerning the reduction of the intraspecies factor. The other scenarios do not reach concern

Dermal contact

conclusion (ii) There is at present no need for further information and/or testing and no need for for risk reduction measures beyond those which are being applied already

Dermal studies with repeated application are not available. Besides the tests described in chapter 4.1.2 only a general notice from occupational use describes principally local irritant reactions of the skin, eyes and respiratory tract. The data demand no classification and are not substantiated enough for raising a concern for repeated dermal contact.

Systemic effects

Inhalation

conclusion (iii) There is a need for limiting the risk; risk reduction measures which are already being applied shall be taken into account

Distinct systemic effects after inhalation or oral administration of vinyl acetate are not reported. The only indicator for systemic effects after repeated inhalation of vinyl acetate could be a decreased body weight gain observed in rats at 2,142 mg/m^3 (600 ppm) and in mice at 714 mg/m^3 (200 ppm) and above, observed in a combined chronic toxicity and carcinogenicity study. This study which was used for the risk assessment of local effects after repeated inhalation serves also for the risk assessment of systemic effects. Based on the reduction of body weight gain the NOAEC of 50 ppm (180 mg/m^3) of the mice is taken for the MOS calculation.

The derivation of the starting point and the reference MOS are identical with the values which are derived for carcinogenicity (values see under endpoint carcinogenicity). The critical exposure level regarding systemic toxicity after repeated inhalation is identified as 17.6 mg/m^3 (90 / 5.1). The highest shift average value for inhalation is reported as 14.6 mg/m^3 for manufacturing of formulations and products of vinyl acetate in scenario 2. Compared with the OEL of 17.6 mg/m^3 the scenario is a borderline case. Conclusion iii is drawn for scenario 2 since there is the uncertainty concerning the reduction of the intraspecies factor. The other scenarios do not reach concern.

Dermal contact

conclusion (ii) There is at present no need for further information and/or testing and no need for for risk reduction measures beyond those which are being applied already

Dermal studies with repeated application are not available. Thus the studies with other routes of application are taken into account. Since a quantitative risk assessment regarding repeated dermal contact is connected with high uncertainties regarding systemic availability, route-to-route extrapolation and the missing of distinct systemic effects, only a rough estimation is done. For this the following considerations regarding the assessment of repeated dermal exposure are taken into account: Neat vinyl acetate (1 mg/m^3) would evaporate within about 10 seconds from skin under usual working conditions of non occlusive exposure. From the experimental data there is no distinct systemic effect described (highest tested dose of 810 mg/kg/day from the drinking water study). Compared with the highest dermal exposure of 6 mg/kg (scenario 2a, use of vinyl acetate monomer) there seems to result no concern for repeated dermal contact.

Mutagenicity

conclusion (ii) There is at present no need for further information and/or testing and no need for for risk reduction measures beyond those which are being applied already

The substance has a mutagenic potential, which is preferentially expressed as clastogenesis. It is unlikely, that the genotoxic potential of vinyl acetate is expressed in germ cells in man, because genotoxicity of vinyl acetate is limited to toxic doses. For vinyl acetate a threshold mechanism of action is assumed.

Carcinogenicity

conclusion (iii) There is a need for limiting the risk; risk reduction measures which are already being applied shall be taken into account

Regarding the carcinogenicity of vinyl acetate, no adequate human data base is available. Long-term inhalation and oral administration of vinyl acetate in experimental animals produced tumors at the primary site of exposure, the surface epithelium of the respiratory tract and the upper gastrointestinal tract. After inhalation a tumor response to vinyl acetate exposure was seen at 600 ppm in rats, for the oral route an increase of tumor rates has been observed at 10,000 ppm. Vinyl acetate carcinogenicity is assumed to be mediated by the metabolic product acetaldehyde. Based on the nonlinear kinetics of intracellular aldehyd dehydrogenase activity there is a marked increase of intracellular acetaldehyde only at high concentrations of vinyl acetate. With reference to this non-linear dose response relationship for the critical metabolite acetaldehyde risk assessment is performed with the MOS approach.

The study, which serves as key study for the risk assessment of carcinogenicity of vinyl acetate is the combined chronic toxicity and carcinogenic study, which was already taken for the risk assessment of repeated dose toxicity. From this study a NOAEC of 50 ppm (180 mg/m^3) is derived and used as a threshold concentration. The experimental NOAEC of 180 mg/m^3 is (1) adapted by a factor of 6/8 to account for differences between the experimental inhalation duration of 6 hours per day and the average working day of 8 hours per day, and (2) is multiplied by a factor of 6.7/10 for activity-driven differences of respiratory volumes in workers. This results in an adjusted inhalation starting point of 90 mg/m^3 (180 • 6/8 • 6.7/10).

The reference MOS would account with the intraspecies differences with a factor of 1.25 – 2.5, the interspecies differences would deal with a factor of 2.5 This would altogether result in a reference MOS of about 3 to 6. The critical exposure level regarding carcinogenicity would then lie between 15 and 30 mg/m^3 (90 / 6 or 3), depending on how big the intraspecies differences are dealt with. The lower value of 15 mg/m^3 is in the same order than the occupational exposure value of 17.6 mg/m^3 (5 ppm), which was set by SCOEL (2005). For pragmatic reasons this value is taken forward in this risk assessment. The SCOEL value corresponds to a reference MOS value of 5.1. For scenario 2 (manufacture of formulations and products), the exposure is 14.6 mg/m^3. Since there is the uncertainty concerning the reduction of the intraspecies factor and the mode of action for carcinogenesis for this borderline scenario conclusion iii is drawn.

Dermal carcinogenicity studies are not available. An oral drinking water study with rats (Umeda et al., 2004a) showed higher incidences of tumor rates at the local site of contact: squamous cell carcinoma in the the oral cavity, esophagus, and stomach, which were considered to be treatment related. Vinyl acetate should be able to reach vivid skin cells and a potential to induce skin tumours cannot be excluded. A quantitative approach is not possible, since a quantitative route to route extrapolation of local effects is generally not performed. For risk characterisation purposes it should be further considered, that the high vapour pressure of vinyl acetate leads to reduced retention time on skin absorption.

The highest dermal exposure value (6 mg/kg/day) was estimated for the use of pure vinyl acetate during manufacture of formulations and products (scenario 2a). The magnitude of this exposure value is also based on the knowledge, that gloves are not regularly worn in small and medium-sized enterprises. The other scenarios have exposure values at least one order of magnitude below (<0.6 mg/kg/day). This is due to a high acceptance of gloves in the large-scale chemical industry (scenario 1) and the fact, that vinyl acetate is only available as a residual monomer (< 2 – 3000 ppm) in scenario 2b and 3.

Based on this information and the fact that especially the high doses led to a significant carcinogenic response in experimental studies, scenario 2a with the highest exposure due to non-effective skin protection is considered to be associated with a significant risk, which should require further specific measures. The other scenarios (scenario 1, 2b, 3) are considered to be of lower concern and a low risk level is assumed.

Reproductive toxicity

Fertility impairment and developmental toxicity

conclusion (ii) There is at present no need for further information and/or testing and no need for for risk reduction measures beyond those which are being applied already

With respect to toxicity for reproduction no human data are available.

Distinct reproduction related adverse effects of vinyl acetate are not reported from a two generation drinking water study with rats for concentrations including 1000 ppm.The developmental toxicity of vinyl acetate has been investigated in rats via oral (drinking water) and inhalation exposure routes during organogenesis. No embryo/fetotoxic or teratogenic effects were observed for the oral route of administration at drinking water concentrations including 5000 ppm. Fetotoxic effects, revealed during inhalation exposure, were confined to high dose levels only, where severe maternal toxicity was observed. In addition, any specific teratogenic potential and/or impairment of embryo/fetal development are not indicated from the same data. Therefore no MOS calculation is performed for this endpoint.

Summary of conclusions for the occupational risk assessment

Risk estimation for vinyl acetate is mainly based on animal inhalation studies and oral studies. 15% inhalative absorption is assumed for the assessment of systemic effects, 50% after oral uptake and 90% absorption after dermal contact. The most pronounced effects of vinyl acetate are local effects after repeated inhalation contact and carcinogenicity. The value of 17.6 mg/m^3 designates the critical exposure level as well for carcinogenicity as repeated dose toxicity after inhalation. Endpoints and scenarios of concern are summarized in the following table.

Table 4.3: Endpoint-specific overall conclusions

Toxicological endpoints		General conclusion	Exposure Scenarios
Acute toxicity	inhalation	ii	
	dermal	ii	
	combined	ii	
Irritation/ Corrosivity	dermal	ii	
	eye	ii	
	acute respiratory tract	ii	
Sensitisation	skin	ii	
	respiratory	ii	
Repeated dose toxicity	inhalation, local	iii	2
	inhalation, systemic	iii	2
	dermal, local	ii	
	dermal, systemic	ii	
	combined, systemic	iii	2
Mutagenicity		ii	
Carcinogenicity	inhalation	iii	2
	dermal	iii	2a
	combined	iii	2[(1)]
Reproductive toxicity	inhalation	ii	
	dermal	ii	
	combined	ii	

[(1)]conclusion iii already results from inhalative and/or dermal exposure, therefore no specific concern for the combined exposure scenario is indicated

Scenario 2 (manufacture of formulations and products), with an exposure value of 14.6 mg/m^3 is a borderline case. Since there is the uncertainty concerning the reduction of the intraspecies factor and the mode of action for carcinogenesis for this borderline scenario conclusion iii is drawn for repeated dose toxicity and carcinogenesis. Skin contact of vinyl acetate should be reduced in scenario 2a (manufacturing of formulations and products, vinyl acetate monomer), even if evaporation of the substance reduces the contribution of dermal exposure.

Consumers

Following the exposure assessment there is no direct exposure of the consumer to vinyl acetate besides of the release of monomers from polymers. Overall exposure to vinyl acetate occurs mainly via inhalation due to emissions from carpets, paints and adhesives. For comparison with acute effects, the estimate for short-term exposure to concentrations of a about 1 mg/m³ from carpets will beused. With regard to chronic effects, the concentration of 0.036 mg/m³ for long-term exposure will be used resulting in an exposure of 9.2 µg/kg bw/d for men, of 4.6 µg/kg bw/d for women, and of 18 µg/kg bw/d for children. The inhalation exposures numbers representing residual monomeric vinyl acetate still overestimate realistic chronic exposure because according to the biochemical data remarkable amounts of vinyl acetate will be metabolized rapidly to acetaldehyde in the olfactory and respiratory epithelium (see chapter 4.1.2.1) thus only very small amounts of vinyl acetate will reach the systemic circulation. Furthermore, the consumer may be exposed to vinyl acetate by using hair setting lotions (1 µg/kg bw/d) by the dermal route and by migration of the substance from plastics coming into contact with foods via oral route. Since this exposure scenario is regulated (see chapter 4.1.1.3) there is no need for MOS calculation.

Acute Toxicity

Following the exposure assessment, consumers are not expected to be exposed to vinyl acetate in the range of doses which can be derived from acute oral or dermal toxicity figures based on animal LD 50 values (oral and dermal: > 3500 mg/kg body weight). Therefore the substance is of no concern in relation to acute oral or dermal toxicity.

The inhalation route of exposure should be of no concern, because in rats vinyl acetate has demonstrated LC50 values of > 14 mg/l/4h. For short-term exposure from carpets concentrations of 0.001 mg/l have been calculated.
Conclusion ii)

Irritation/Corrosivity

Vinyl acetate causes only mild irritation to the skin and eyes of rabbits, but causes severe irritation in the respiratory tract of rats. Human data on irritation/corrosivity caused by vinyl acetate are not available.

Following the exposure assessment it can be assumed that consumers are exposed only to such concentrations which are far below the effective concentrations.
Conclusion ii)

Sensitization

Data obtained from a Buehler Test demonstrate that vinyl acetate (commercial grade) is a moderate skin sensitizer. The results of a Local Lymph Node Assay confirm the weak to moderate effects in the Buehler Test, but do not warrant classification and labelling.

No reports of allergic contact dermatitis caused by vinyl acetate from routine patch testing or experimental studies in man are available. Furthermore, no direct information is available from studies in humans on respiratory sensitization. In view of the widespread occupational use, the absence of any reports suggests that vinyl acetate may not be a respiratory sensitizer.
Conclusion ii)

Repeated dose toxicity/Non-neoplastic lesions

Following the exposure assessment there may be chronic exposure to vinyl acetate resulting from release of residual monomers out of polymers.

The major toxic effects after prolonged inhalation of vinyl acetate in experimental animals were lesions of the surface epithelium of the upper and lower respiratory tract. Degeneration, regenerative/reparative processes, inflammation, hyperplasia and metaplasia were noted in the nasal mucosa as non-neoplastic effects. These effects were most pronounced in the olfactory epithelium occurring at 200 ppm in rats and mice during and at the end of a 2-year exposure period. Lesions of the respiratory epithelium were seen in mice exposed to 600 ppm during and at the end of 2 years, whereas rats demonstrated lesions at this site only at a high concentration of 1000 ppm (4 week study). Characteristic alterations of the larynx and trachea of mice in the 600 ppm groups were hyperplasia and metaplasia along with desquamation and

fibrosis in the trachea. Similar changes of the bronchial and bronchiolar airways were reported for rats and mice at this concentration at the end of the 2-year exposure period. In addition, clinical signs of non-specific toxicity and irritation were evident, but no relevant toxic effect on any organ could be identified. The NOAEC for local toxic effects on the respiratory tract of 50 ppm (178.5 mg/m³) was derived from the 2-year studies on rats and mice. Based on growth retardation in rats of the 600 ppm groups and due to hunched posture in mice of the 200 ppm groups, the NOAEC for systemic toxicity was considered at 50 ppm for mice (178.5 mg/m^3) and 200 ppm for rats (714 mg/m³).

No specific organ toxicity was recorded after repeated oral administration of vinyl acetate with drinking water to rats and mice. A subchronic 13-week study revealed a slight (non-significant) reduction of food consumption and growth retardation in male rats at 5000 ppm (684 mg/kg bw/d).

For the decision on the appropriateness of MOS, the following major aspects should be taken into account:

- intra- and interspecies variation

The results of PBPK modeling are taken forward for consideration on the appropriate adjustment factors. As vinyl acetate is acting locally, a systemic metabolism has not to be considered, which reduces the interspecies factor from 10 (default) to 2.5. Remaining uncertanties in toxicodynamic differences are recognized, i. e. humans could be more sensitive than rats towards local toxicity of vinyl acetate metabolites which could not be excluded due to the lack of (primarily human) data. Thus, for risk charaterization an interspecies adjustment factor of 2.5 is established. Concerning intraspecies variability the same consideration as for interspecies extrapolation applies. No systemic metabolism has to be taken into consideration, reducing the intraspecies adjustment factor to 2.5.

Following the exposure assessment, the consumer may be exposed to vinyl acetate via inhalation, whereas oral and dermal exposures are assumed of minor importance.

a) Inhalation route

The NOAEC used for the discussion of the MOS regarding exposure from carpets is derived from a 2-year inhalation study on rats. Because vinyl acetate acts primarily at the nasal cavity, systemic effects have not been considered. Moreover, the NOAEC for systemic effects was considered to be 714 mg/m^3 for rats and 178 mg/m³ for mice in the same study.

b) Oral route

The oral route is not relevant for risk characterization (see introductory remarks).

c) Dermal route

Following the exposure assessment, the consumer may be exposed dermally to vinyl acetate via usage of hair setting lotions. The estimated dermal body burden (1 µg/kg bw/d) with an

assumed absorption of 100% is compared with a NOAEL from an oral 90-day study due to the lack of a dermal study.

MOS for Inhalation exposure scenario

Long-term exposure to 0.036 mg/m³ vinyl acetate is assumed to result via emission from carpets. The margin of safety for non-neoplastic effects between the

measured exposure level of 0.036 mg/m^3

and the

NOAEC for local irritation effects of 178 mg/m^3

is judged to be sufficient taking into account the nature of the observed effects (degenerative lesions of the olfactory mucosa) and the fact that no steep dose-response relationship is observed for the these effects. Considering the short-term exposure, see section Acute toxicity. Conclusion ii)

MOS for Dermal exposure scenario

The calculation of the dermal exposure due to hair setting lotions leads to an external exposure of 1 µg/kg bw/d. The margin of safety between the

external dermal exposure 1 µg/kg bw/d

and the

oral NOAEL of 684 mg/kg bw/d

is judged to be sufficient.
Conclusion ii)

Mutagenicity

Vinyl acetate is not mutagenic to bacteria, but it induces chromosomal aberrations, gene mutations and SCE in several tests with mammalian cells from different sources in culture. Furthermore, at high concentrations the formation of DNA-protein-crosslinks and DNA-DNA-crosslinks is shown with mammalian cells.

The in vivo genotoxicity of vinyl acetate appears to be limited to toxic doses. Therefore, the substance may express its genotoxic potential only when defence mechanisms are overloaded and thus it may be reasonable to assume a threshold mechanism of action for vinyl acetate genotoxicity.

Taking into account the low consumer exposure (in the range of up to 20 µg/kg bw/d) based on the present knowledge it may be concluded that there is presently no concern regarding in vivo mutagenicity. Conclusion ii)

Carcinogenicity

In cancer studies, vinyl acetate inhalation induced an increased number of nasal tumors (mainly papillomas and squamous cell carcinomas) in various regions of the nasal mucosa of rats. The total incidence was significantly increased at a concentration of 600 ppm (2142 mg/m^3) but a single papilloma already developed at 200 ppm. Thus, the NOAEC of 50 ppm (178 mg/m^3) will be used for the risk characterisation. No significant tumor response was seen in a mice cancer bioassay. Occasionally single squamous cell tumors occurred at other sites of the respiratory tract in rats and mice.

For the oral route a marked increase of tumor rates has been observed at 1000 ppm (rat (offspring); 70 mg/kg bw/d), at 5000 ppm (mouse; 750 mg/kg/d) and at 10000 ppm (male rat 442 mg/kg bw/d, female rat 575 mg/kg bw/d). Due to limitations in the study design in the studies of Maltoni et al. (1997) and Minardi et al. (2002), the study of Umeda et al. (2004a) is considered of higher predictivity (cf. 4.1.2.8). For lower doses, there is concern that occasional findings of tumors of the same types that have been observed at high doses and which might also be related to vinyl acetate exposure. Thus, the lowest concentration suspected to be carcinogenic was 400 ppm for the oral route (LOAEL, male rat 21 mg/kg bw/d, female rat 31 mg/kg bw/d, Umeda et al., 2004a). Clearly tumor free dosages were not established in carcinogenicity studies for the oral route. Thus, 400 ppm (21 mg/kg bw/d male rat) is proposed as LOAEL for oral risk characterisation. Since carcinogenicity is a critical toxicological endpoint a risk characterisation for the oral route was calculated.

Vinyl acetate exposure produced tumors at the site of first contact along the exposure routes by inhalative and oral uptake. A thresholded mode of carcinogenic action is thought to be active. Uncertainties exist in the proposed mode of action and should taken into account.

MOS for Inhalation exposure scenario

Long-term exposure to 0.036 mg/m³ vinyl acetate is assumed to result via emission from carpets. The margin of safety for non-neoplastic effects between the

measured exposure level of 0.036 mg/m^3

and the

NOAEC 178 mg/m^3

is judged to be sufficient.
Conclusion ii)

MOS for Oral exposure scenario

The oral route is not relevant for risk characterization (see introductory remarks).

Reproductive toxicity

Since no hazards have been identified regarding fertility and developmental toxicity a risk characterisation should not be performed. This decision is further supported by the fact that the systemic availability of vinyl acetate is very low.

Humans exposed via the environment

Indirect exposure to humans via the environment occurs mainly by air. Following the local scenario data (at a point source) a maximum intake of a total daily dose of 0.036 mg/kg bw/d is calculated. For the regional scenario, the respective figure is 0.00247 µg/kg bw/d.
The main route of indirect exposure of both scenarios (local and regional) is the intake via inhalation of air. Therefore the local concentration of 0.288 mg/m^3 for site 26 was selected and used for risk characterisation.

Repeated dose toxicity
Inhalation
Local effects on the respiratory tract are not to be expected because of the low concentrations in the air of 0.288 mg/m^3 (local exposure). The NOAEC for local toxic effects on the respiratory tract of 50 ppm (178.5 mg/m^3) was derived from the 2-year studies on rats and mice.
MOS for Inhalation exposure scenario

The margin of safety for non-neoplastic effects between the

estimated exposure level of 0.288 mg/m^3

and the

NOAEC 178 mg/m^3

is judged to be sufficient.
Conclusion ii)

Mutagenicity
Vinyl acetate is not mutagenic to bacteria, but it induces chromosomal aberrations, gene mutations and SCE in several tests with mammalian cells from different sources in culture. Furthermore, at high concentrations the formation of DNA-protein-crosslinks and DNA-DNA-crosslinks is shown with mammalian cells. The in vivo genotoxicity of vinyl acetate appears to be limited to toxic doses thus it may be reasonable to assume a threshold mechanism of action for germ cell mutagenicity.

Taking into account the exposure estimates resulting for a point source from a worst case calculation and from regional background concentrations it may be concluded that there is presently no concern regarding in vivo mutagenicity.
Conclusion ii)

Carcinogenicity
Vinyl acetate inhalation induced an increased number of nasal tumors (mainly papillomas and squamous cell carcinomas) in various regions of the nasal mucosa of rats (cf. 4.1.2.8, 4.1.3.3). The total incidence was significantly increased at a concentration of 600 ppm (2142 mg/m^3) but a single papilloma already developed at 200 ppm. Thus, the NOAEC of 50 ppm (178 mg/m^3) will be used for risk characterisation purposes.
MOS for Inhalation exposure scenario

The margin of safety for neoplastic effects between the

estimated exposure level of 0.288 mg/m^3

and the

NOAEC 178 mg/m^3

is judged to be sufficient. Conclusion(ii)

Reproductive toxicity

Since no hazards have been identified regarding fertility and developmental toxicity a risk characterisation should not be performed. This decision is further supported by the fact that the systemic availability of vinyl acetate is very low.

Combined exposure

[click here to insert text]

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

Vinyl acetate is highly flammable. Adequate worker protection measures must be observed. Risk reduction measures beyond those which are being applied already are not considered necessary.

5 RESULTS

5.1 ENVIRONMENT

Aquatic compartment (incl. sediment)

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

A risk to the local or regional aquatic compartment (surface water and sediments) and to sewage treatment plants was not identified for production and processing of vinyl acetate. This conclusion applies to all sites and the generic scenario for unknown sites.

Terrestrial compartment

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

This conclusion applies to all known production and processing sites.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

This conclusion applies to the generic processing scenario for the local main source. The unknown processing sites account for a missing tonnage of 325,000 t/a (41 % of the total production volume of 800,000 t/a). Risk reduction measures should be considered for all facilities with a vinyl acetate processing capacity exceeding 20,000 t/a. Sites already applying advanced techniques would not require further consideration of risk reduction measures.

Atmosphere

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Based on a qualitative risk characterisation, no unacceptable risk for the atmosphere is expected from vinyl acetate. The substance is rapidly removed from air by chemical breakdown, adsorption to airborne particles or aerosols, and wet deposition. Furthermore, air concentrations indicate a negligible risk with regard to ecotoxicity.

Secondary poisoning

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Non compartment specific effects (secondary poisoning) of vinyl acetate are not expected as there is no indication that the substance has potentially bioaccumulative properties.

Marine assessment including PBT assessment

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

VAM does not meet the PBT/vPvB criteria. A risk for the regional or local marine environment is not expected.

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

Workers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

This conclusion applies to the endpoint of carcinogenicity after inhalation and dermal contact and repeated dose toxicity after inhalation. Skin contact of vinyl acetate should be reduced at scenario 2a (manufacturing of formulations and products, vinyl acetate monomer), even if evaporation of the substance reduces the contribution of dermal exposure.

On the background of cancer risks and repeated dose toxicity, air concentrations of vinyl acetate at the workplace should be controlled to a level in the range of 17.6 mg/m^3 (critical exposure level). Conclusion iii is derived for repeated dose toxicity after inhalation for scenario 2 (manufacturing of formulations and products). This scenario with an exposure value of 14.6 mg/m^3 is a borderline case. Since there is the uncertainty concerning the reduction of the intraspecies factor and the mode of action for carcinogenesis for this borderline scenario conclusion iii is drawn.

Consumers

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Humans exposed via the environment

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

5.2.2 Human health (risks from physico-chemical properties)

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.