EUROPEAN COMMISSION

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METHYL ACETATE

CAS No: 79-20-9

EINECS No: 201-185-2

Summary Risk Assessment Report

2003 **Special Publication I.03.102**

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SUMMARY RISK ASSESSMENT REPORT

Final report, 2003

Germany

The risk assessment of methyl acetate has been prepared by Germany on behalf of the European Union.

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Date of Last Literature Search: **2002**
Review of report by MS Technical Experts finalised: **2001**
Final report: **2003**

PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substance methyl 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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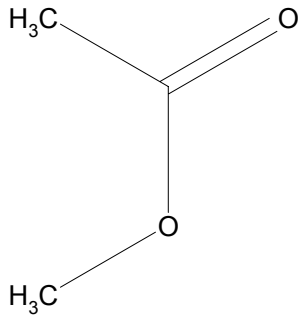
1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS Number: 79-20-9
EINECS Number: 201-185-2
IUPAC Name: Methyl acetate
Synonyms: Acetic acid methyl ester
Molecular weight: 74.08 $g \cdot mol^{-1}$
Molecular formula: $C_3H_6O_2$
Structural formula:



1.2 PURITY/IMPURITIES, ADDITIVES

Purity: > 99%
Impurities: acetaldehyde
methanol
water
acetic acid
acetaldehydedimethylacetale
methylformiate
acetone
ethylacetate
vinylacetate

Dependent on the production process, in addition to the pure substance, a solvent mixture of methyl acetate is formed containing approx. 15 up to 30 % acetone, < 8 % methanol, 0.5 up to 1.5 % water and < 0.05 % acetic acid.

1.3 PHYSICO-CHEMICAL PROPERTIES

Table 1.1 Summary of physico-chemical properties

Property	Value
Physical state	liquid at 20 °C
Melting point	- 98.1°C
Boiling point	57°C at 1,013 hPa
Relative density	0.928 at 20°C
Vapour pressure	133 hPa at 9.4°C 533 hPa at 40°C 217 hPa at 20°C
Water solubility	250-295 g/l at 20°C
Partition coefficient Log Pow	0.14 (calculated) 0.18 at 20°C
Flash point	-10°C
Autoflammability	475°C
Flammability	highly flammable
Explosive properties	not explosive
Oxidising properties	no oxidising properties
Surface tension	37.3 mN/m at 20°C (conc. 148.2 g/l in water)

The data given in the table are related to the pure substance (> 99% purity)
Vapour pressure:
- the value at 20°C can also be interpolated from the literature data and results in 221 hPa which is in good agreement with the given value of 217 Pa in the safety data sheet of the Hoechst AG;
- the value of 217 hPa was used for all further calculations.

1.4 CLASSIFICATION

Classification

F; R11	Highly flammable
Xi; R36	Irritating to eyes
R66	Repeated exposure may cause skin dryness or cracking
R67	Vapour may cause drowsiness and dizziness

Labelling

F; Xi
R: 11-36-66-67
S: (2-)16-26-29-33

According to the data presented below and the criteria of Directive 93/21/EEC, methyl acetate has not to be classified as dangerous for the environment.

Methyl acetate is classified according to water-hazard class 1 (slightly hazardous to water).

In the general administrative provisions relating to the (German) federal law on the prevention of immissions - technical regulations on air pollution control (technical regulations on air pollution control of 27.02.1986) - methyl acetate is named in Annex E and classified according to class II (at a mass flow of 2 kg/h or more, the mass concentration must not exceed 0.1 g/m^3).

2 GENERAL INFORMATION ON EXPOSURE

According to the information from the available IUCLID data sets there are four production sites of methyl acetate in the EU. No information is available on possible imports.

The production quantity is given as 30,000 t/a for 1993.

Dependent on the production process, approximately 99.5% pure methyl acetate or a solvent mixture containing 60 to 75% methyl acetate results in the production of methyl acetate. In addition to methyl acetate, the solvent mixture which occurs contains approximately 15 to 30% acetone, <8% methanol, 0.5 to 1.5% water and <0.05% acetic acid.

In Germany, approximately 70% of the methyl acetate which is produced is used as a solvent (e.g. in adhesives, paint systems, in cosmetic agents and cleaning products). A further quantity (approx. 10%) of the substance is used as an intermediate in the manufacture of plant protection products and vitamins. The remainder (20%) is exported and used as an intermediate for the production of sweeteners. The destination is unknown. Further information on the use of the substance is not available for the EU.

It can be assumed that the use pattern of methyl acetate in Germany is also applicable to the EU. The special conditions which relate to Germany will be considered in the exposure consideration for the area concerning the use of the substance. However, attention must be drawn to the fact that comparable local exposures to methyl acetate during use of the substance are also to be expected in the other EU member states.

The use of methyl acetate as a solvent in adhesives and paint systems is described in the Danish Product Register of January 1995. 6 products with a content of 0 to 1%, 8 products with a content of 1 to 10% and 14 products with a content of 10 to 80% are known. The quantity of the substance used in the products is around 3 t/a.

The substance is also listed in the Swedish Product Register for 1993. Approximately 4 to 6 t/a methyl acetate are used as a solvent and in adhesives. Methyl acetate is not included in the Norwegian Product Register for 1994.

Products containing methyl acetate are used by consumers.

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

Releases into the hydrosphere and atmosphere are expected from production, processing and use as a solvent via the wastewater and the exhaust air.

Exposure of the terrestrial compartment is expected due to deposition from atmosphere.

General characteristics of methyl acetate which are relevant for the exposure assessment are:

- estimated atmospheric half-life of 50.4 days,
- moderate volatility because of the low Henry's law constant (6.43 $Pa \cdot m^3 \cdot mol^{-1}$),
- hydrolysis half-lives between 63 and 627 days were calculated; therefore hydrolysis should not represent a significant elimination process,
- methyl acetate can be classified as "readily biodegradable" in surface water,
- no accumulation potential is expected due to the measured log Pow of 0.18 (Koc 12.99 l/kg).

According to the physical properties, the target compartments are the atmosphere (69.3 %) and the hydrosphere (30.7%).

Aquatic compartment (incl. sediment)

For the environmental exposure assessment site-specific scenarios are used for calculating the PECs in surface waters for production. Local concentrations for production or use as an intermediate range from 0.07 to 4.6 µg/l.

Since no quantitative breakdown of the application is available an even distribution between the uses is assumed. The maximum aquatic local PECs for continuous discharge of 278 µg/l are calculated for the formulation of household chemicals, adhesives, paints and lacquers.

No specific information is available for the calculation of the $Clocal_{effl}$. The highest effluent concentration for wastewater treatment plants was calculated as 2.78 mg/l for the formulation of paints, lacquers, adhesives and household chemicals and 0.23 mg/l for processing of paints in paint shops (e.g. car painting).

Data on the occurrence in sediment do not exist for methyl acetate. According to the known physico-chemical properties, there is no indication that methyl acetate accumulates in sediment.

Atmosphere

Since the exposure data submitted by the companies for production and processing cannot be verified, the releases into the atmosphere are calculated using the A- and B-tables (TGD, Chapter 3, Appendix I). The highest calculated air concentration is around 232 $\mu g/m^3$ for the production of methyl acetate.

Terrestrial compartment

Methyl acetate is expected to enter the soil as a result of deposition from the atmosphere. In this regard the point source of the production and the use as an intermediate of the substance involving the highest amount of air pollution are considered. The highest deposition rate is due to the production of methyl acetate, implying soil concentrations amounting to 20 µg/kg (TS) and 59 µg/l soil pore water.

Secondary poisoning

Since there is no indication of methyl acetate possessing a bioaccumulation potential, a risk characterisation for exposure via the food chain is not necessary.

3.2 EFFECTS ASSESSMENT

For methyl acetate only short-term tests are available. In a test with fish a 96-hour LC_{50} of 320 mg/l was obtained for *Pimephales promelas*. For *Daphnia magna* a 48-hour LC_{50} of 1,027 mg/l was available. In a study with *Scenedesmus subspicatus* no effects could be observed after 72 hours at a concentration of 120 mg/l.

Using an assessment factor of 1,000, a PNEC of 320 µg/l was determined on the available data basis.

No ecotoxicological data are available for terrestrial organisms. In approximation, the aquatic PNEC can be used for the purpose of a risk assessment for the terrestrial compartment and compared with the concentration determined for the soil pore water: $PNEC_{soil}$ = 320 µg/l (soil pore water).

For the determination of the $PNEC_{WWTP}$ for municipal WWTPs, the result with *Pseudomonas putida* (16-hour EC_{10} = 1,830 mg/l) can be used. With an assessment factor of 1**,** a PNEC of 1,830 mg/l can be calculated.

3.3 RISK CHARACTERISATION

3.3.1 Aquatic compartment (incl. sediment)

For the aquatic compartment, the risk characterisation based on site-specific scenarios for production and/or processing of methyl acetate leads for all sites to a PEC/PNEC ratio <1. **Conclusion (ii)**.

For the formulation of household chemicals, use of household chemicals, formulation of paints and lacquers, formulation of adhesives, processing of paints and lacquers in paint shops (e.g. car painting) and use of paints and lacquers in the private domain the PEC/PNEC ratios are <1. Therefore, no risk is to be expected for the environment from these life-cycle steps. **Conclusion (ii)**.

Taking into consideration a $PNEC_{WWTP}$ of 1,830 mg/l, a $Clocal_{effl}$/PNEC ratio of 0.0015 and 0.00012 is calculated for the formulation of paints, lacquers, adhesives and household chemicals and the processing of paints in paint shops (e.g. car painting). Since the $Clocal_{effl}$/PNEC ratio <1, there is no risk to the microorganisms in the WWTP. **Conclusion (ii)**.

No data on the occurrence in sediment or investigations into the effect on benthic organisms are available in connection with methyl acetate. According to the available physico-chemical properties of the substance, there is no indication that methyl acetate accumulates in sediment. Consequently, there is no need for a risk consideration for this compartment. **Conclusion (ii)**.

3.3.2 Atmosphere

Due to the atmospheric half-life ($t_{1/2}$ = 74 to 94 days), abiotic effects on the atmosphere, such as global warming and ozone depletion, are not to be expected in connection with methyl acetate. The highest calculated air concentration is around 232 µg/m^3 for the production of methyl acetate. Since no data are available on the ecotoxicological effect of the substance in connection with this environmental compartment, it is not possible to undertake a quantitative assessment of this environmental compartment. On the basis of the available information on the substance, tests are not considered to be necessary. **Conclusion (ii)**.

3.3.3 Terrestrial compartment

Releases into the terrestrial compartment as a result of deposition from the atmosphere are to be expected. The highest deposition rate is due to the production of methyl acetate, implying soil concentrations amounting to 20 µg/kg (TS) and 59 µg/l soil pore water.

Since no ecotoxicological data are available for terrestrial organisms, in approximation, the aquatic PNEC (320 µg/l) is considered for the purpose of the risk assessment of the terrestrial compartment and compared with the concentration determined for the soil pore water. With these data a PEC/PNEC ratio of 0.18 is calculated. Therefore, there is no indication of a risk to the terrestrial environmental compartment at the present time. **Conclusion (ii)**.

3.3.4 Secondary poisoning

Since there is no indication that methyl acetate possesses a bioaccumulation potential, a risk characterisation for exposure via the food chain is not necessary.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 Occupational exposure

Methyl acetate is used as a chemical intermediate and as a solvent in different formulations. In Germany, about 10 % of the produced methyl acetate is further processed as a chemical intermediate to methanol, acetic acid, vitamins and plant protection products, 70% is used as a solvent in paints, adhesives, cleansers etc., and about 20% is exported.

Detailed information on the production volumes is given in Section 2.

Based on the available information the following relevant occupational exposure scenarios are to be expected:

- production and further processing as a chemical intermediate,
- formulation of preparations,
- use of formulations (paints, adhesives, cleansers, no spray techniques),
- use of formulations (spraying paints and adhesives),
- use of formulations for flooring works,
- use of formulations (nail polish remover) in the cosmetic sector.

The following occupational exposure limits are established for methyl acetate.

Norway (1996)	305 mg/m^3
Sweden (2000)	450 mg/m^3
Denmark (2000)	455 mg/m^3
US: ACGIH, Italy (2000)	606 mg/m^3
US: OSHA (1993), Austria (2001), France (1999), Finland (1999), Germany (2001), Ireland (1999), Switzerland (2001), The Netherlands (2001)	610 mg/m^3
Belgium (1999)	615 mg/m^3
Spain (2000), UK (2001)	616 mg/m^3

and the following short-term exposure limits:

US: ACGIH, Italy (2000)	757 mg/m^3
US: OSHA (1993), France (1999), Ireland (1999)	760 mg/m^3
Belgium (1999)	768 mg/m^3
Finland (1999), Spain (2000), UK (2001)	770 mg/m^3
Sweden (2000)	900 mg/m^3
Austria (2001), Switzerland (2001)	1,220 mg/m^3

In Germany the short-term exposure limit is 2,440 mg/m^3 (4 · MAK, 15-min average).

The exposure assessment is based on measured data and literature data, expert judgement 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. If sufficient numbers of measured results are available, the 90th percentiles are taken as a measure for the reasonable worst-case situations.

With regard to dermal exposure, measured results are not available. For most occupational exposure scenarios, the regular use of suitable PPE (Personal Protective Equipment) at the workplace is not probable. Therefore, actual dermal exposure is generally assessed based on the EASE model without considering that PPE might be worn by a part of the exposed collective. In case of methyl acetate, the high volatility of the substance reduces dermal exposure considerably. Based on physico-chemical calculations, the retention time of pure methyl acetate amounts to 6 seconds (coverage 1 mg/cm^2). As for the pure substance, short retention times are expected for formulations as well. In this case, quantitative calculations cannot be made due to the complex composition of the mixtures in use. In general, dermal exposure is assessed as exposure to part of hands and forearms.

The results for the different scenarios are summarised in **Table 4.1**. More detailed information on inhalation exposure is given below.

Chemical industry

For the large-scale chemical industry, it is assumed that the production and further processing of methyl acetate is mainly performed in closed systems. Exposure occurs during certain activities in the manufacturing and further processing (Scenario 1). Most of the measured results were given as below the detection limit, which was set relatively high at 61 mg/m^3 (exposure estimate for Scenario 1). The basis for this exposure assessment is limited, because only one out of three producers submitted data. Therefore, for companies which did not submit any data in default of workplace measurements, inhalation exposure is assessed in application of the EASE model (Scenario 2). Similar exposure situations are assumed for the cosmetic industry (Scenario 3).

Formulation of the substance to paints, lacquers, adhesives and cleansers (Scenario 4) may occur in the large-scale chemical industry as well as in small and medium sized companies, where possibly lower levels of protection than the large-scale chemical industry are realised. The exposure levels are regarded to be appropriate for the small and medium sized companies.

Use of formulations

Based on the available information, formulations containing methyl acetate are used as adhesives, paints, lacquers and cleansers in different industrial and skilled trade areas. The formulations are e.g. used for spraying and coating techniques. For Scenarios 5–11, sufficient sets of data are the basis for the exposure assessment. The provided measurement data originate from different branches. For some scenarios, higher 8-hour TWA were measured at workplaces with LEV (Local Exhaust Ventilation) than at workplaces without LEV. For a better understanding, it should be kept in mind, that occupational exposure levels at similar workplaces depend e.g. on the level of technical protection (here: LEV), the technique of application, the concentration of methyl acetate and the amount of the substance in use. Often, if handling large amounts of a substance is required, workplaces are equipped with LEV, whereas workplaces at which small amounts are handled are possibly not equipped with LEV.

This might lead to the situation, that exposure is higher at workplaces with LEV than at those without LEV. The corresponding exposure scenarios are divided into subscenarios in order to make clear that LEV as a single measure is not appropriate to reduce exposure considerably. Changes of technology, of quantities or of concentrations have to be considered in addition.

Methyl acetate may be a component of cosmetic products. The corresponding exposure levels are assessed using the EASE-model (Scenario 12).

Summary of exposure data

The results for the different scenarios are summarised in **Table 4.1**. All data in this table are to be regarded as representing reasonable worst-case situations.

Table 4.1 Summary of exposure data

Exposure scenario	Duration and frequency of activities relevant for exposure	Inhalation exposure Shift average [mg/m³]	Dermal exposure Shift average [mg/p/day]
Chemical industry			
1) Manufacture and further processing as a chemical intermediate	shift length, daily	< 61 (detection limit)	42 - 420 [2, 3)]
2) see above, model estimate		31 – 154 [1)]	
3) Production of cosmetics	2 h (assumed), daily	8 – 39 (EASE)	42 – 420 [2, 3)]
4) Production of formulations (paints, lacquers, adhesives, cleanser)	not known [4)]	294 (90th perc., without LEV) 175 (90th perc., with LEV)	42 – 420 [2, 3)]
Use of formulations (paints, adhesives, cleansers) - no spray techniques			
5) Metal treatment, electro-engineering, wood treatment, 20% methyl acetate in diluted cleansers	shift length (assumed), daily	18 (90th perc., without LEV) 137 (90th perc., with LEV)	26 – 260 [5, 6)]
6) Casting machine, printing machine, mainly within the treatment of wood and metals, (assumed 60% methyl acetate)	shift length (assumed), daily	84 (90th perc., without LEV) 46 (90th perc., with LEV)	25 - 250 [5, 6)]
7) Plastic and plastic foam treatment (assumed 60% methyl acetate)	shift length (assumed), daily	18 (90th perc., without LEV) 30 (90th perc., with LEV)	25 –250 [5, 6)]
8) Production of shoes (assumed 60% methyl acetate)	shift length (assumed), daily	17 (90th perc., without LEV) 23 (90th perc., with LEV)	13 - 125 [5, 6)]
9) Pulp and paper production (assumed 60% methyl acetate)	shift length (assumed), daily	205 (90th perc.)	50 – 500 [5, 6)]
Use of formulations (paint, adhesives cleansers) - spray techniques			
10) Spraying of paints, lacquers, adhesives (assumed 40% methyl acetate)	shift length (assumed), daily	81 (90th perc., without LEV) 56 (90th perc., with LEV)	78 – 780 [5, 6)]

Table 4.1 continued overleaf

Table 4.1 continued Summary of exposure data

Exposure scenario	Duration and frequency of activities relevant for exposure	Inhalation exposure Shift average [mg/m³]	Dermal exposure Shift average [mg/p/day]
Other uses			
11) Flooring works, building trade (assumed 50% methyl acetate)	shift length (assumed), daily	768 (90th perc., without LEV)	420 – 2,100 [5, 6)]
12) Use of cosmetics (nail lacquer remover) (assumed 15 % methyl acetate)	2 h (assumed), daily	50 – 130 (EASE, expert judg.) [7)]	160 – 470 [5, 6)]

1) EASE estimation for those companies which did not submit any measurement data.
2) Exposure assessment based on expert judgement and on model estimates (EASE model).
3) The EASE estimate is largely reduced because of the short duration time of dermal exposure. The retention time of pure methyl acetate is calculated to 6 seconds (order of magnitude) independent on the use of gloves (non-occlusive exposure).
4) Daily duration of exposure depends on the production volume.
5) Exposure assessment based on model estimates (EASE model, assumption: without gloves).
6) Gloves are not regularly worn. 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 methyl acetate in mixture the retention time cannot be calculated because of the complex composition of the mixtures and their specific drying behaviour.
7) Rough estimation on the enrichment of the volatile substance in the vapour compared to the liquid

4.1.1.2 Consumer exposure

In Germany, methyl acetate is known to be used as a component of all-purpose adhesives (content of methyl acetate 50%), of carpet adhesives (content up to 20%) and of parquet adhesives (content up to 13%), as a diluent for adhesives (content 40%), and in addition as a component of nail varnish removers (content of 15%).

Inhalation exposure

For the assessment of the consumer exposure via inhalation, a computer simulation with the aid of the US EPA model SCIES was used estimating the exposure under different conditions with house/room air exchange rates ranging from 0.1 to 0.5 times per hour.

Exposure from all-purpose adhesives

Under conditions of use (10 g all-purpose adhesive in a room of 60 m^3, content of methyl acetate 50%, 5 times per week for 1 hour each**)**, an exposure of the consumer to methyl acetate will result within the range of 1.06 mg/kg bw/d (0.2 room air exchanges/hour). If a child of 20 kg bw uses this adhesive under the conditions indicated above, exposure will also be within the range of 1-10 mg/kg bw/d (0.2 room air exchanges/hour) (reasonable worst case).

Furthermore, as a second reasonable worst-case scenario, it is assumed that a batch of 50 g will be used once a week under the conditions indicated above. Exposure of the consumer will then also be within the range of 1-10 mg/kg bw/d (0.2 room air exchanges/hour).

Under conditions of use of all-purpose adhesives containing methyl acetate, the inhalation exposure of the consumer per event was calculated to reach a peak concentration up to 39 mg/m^3 assuming a room ventilation rate of 0.2 air exchanges per hour (average concentration during use: 26 mg/m^3).

Exposure from carpet adhesives

Under conditions of use of 750 g/m^2 carpet adhesive (with a content of methyl acetate of 20%) in a room with a floor area of 25 m^2 and a volume of 60 m^3, a single application per year for 2 hours each, the consumer will be exposed to an average concentration of 11,000 mg/m^3 per event assuming a room ventilation rate of 0.5 air exchanges per hour. A peak concentration up to 15,000 mg/m^3 is calculated. A dose rate of 1.14 mg/kg bw/d would result as yearly average from this exposure.

Exposure from parquet adhesives

Under conditions of use of 1 kg/m^2 parquet adhesive in a room of 25 m^2 floor area and a volume of 60 m^3 (content of methyl acetate 13%), a single application per year for 4 hours each, the consumer will be exposed to an average concentration of about 6,040 mg/m^3 per event assuming a room ventilation rate of 0.5 air exchanges per hour. A peak concentration of 7,860 mg/m^3 has been calculated. A dose rate of 0.94 mg/kg bw/d would result as a yearly average from this exposure.

Exposure from nail varnish removers

For an assessment of the inhalation exposure of the consumer to methyl acetate when using nail varnish remover (reasonable worst case), a daily use of 0.25 ml of a nail varnish remover (containing 15% methyl acetate) has been assumed. Hence, an amount of 37.5 mg methyl acetate will be applied to the nails. A maximum peak concentration of methyl acetate after use has been estimated to be 0.039 mg/m^3 (with the assumption that the user will stay in the room of use). According to SCIES calculations, the exposure amounts to 0.5 mg per day which would result in a dose rate of 0.008 mg/kg bw/d.

Total inhalation exposure of the consumer

The cumulative inhalation exposure of the consumer by methyl acetate calculated for all kinds of use would be in the range of < 3 mg/kg bw/d when the products are used as intended.

Dermal exposure

Exposure from glues

Dermal exposure may occur during use of methyl acetate containing adhesives and glues that are recommended for hobby and household use. It can be assumed that the amounts used are in a range of less that 10 g, normally a few drops. It is possible, that these drops can come into contact with skin, e.g. by distributing the glue on surface that is intended to be glued. For this scenario, an exposure can be estimated due to the formula given in the TGD for dermal exposure. Because of the uncertainty of the assumptions, distributions have been estimated with a probabilistic approach taking a Monte-Carlo simulation (software: @RISK) instead of point estimates.

According to these calculations, the daily dermal exposure by using methyl acetate containing glues would result in 0.4 (minimum) to 5.9 (maximum) mg/kg bw/d, with a most probable exposure (median) of 1.4 mg/kg bw/d. It should be considered, that this amount is correct only for a few minutes because of drying of the glue. Thus, in fact, the dermal exposure would be much lower.

Exposure from nail varnish removers

The reasonable worst case is based on a daily use of 0.25 ml of nail varnish remover (content 15%) resulting in an application of 37.5 mg methyl acetate per day to the nails. A time quantitative calculation of the absorbed amount of methyl acetate is not possible. Due to the high-vapour pressure of the substance resulting in a short retention time on the nails and assuming that absorption through the nails is very low the dermal exposure of the consumer is considered to be negligible.

Oral exposure

Within the scope of German foods legislation, methyl acetate could be used as an extraction solvent for caffeine, irritating substances, etc. and in the manufacture of sugar from molasses.

Within the legal frame, when consuming 50 g coffee per day, the consumer could be orally exposed to methyl acetate in the range of 10-100 µg/kg bw/d. When consuming 100 g sugar manufactured from molasses per day, the oral exposure would be in the range of 1-10 µg/kg bw/d.

Exposure to methyl acetate will also occur due to its presence in food as a natural flavouring substance, e.g. in bananas and other fruit, in butter, olive oil and alcoholic beverages. The oral exposure from food consumption is estimated to be in the range of 1-10 mg/kg bw/d.

4.1.1.3 Humans exposed via the environment

In accordance with the TGD, the indirect exposure of humans to methyl acetate via the environment, e.g. via food, drinking water and air, must be determined. In the form of a worst-case scenario, the most significant point source (in this case the formulation of household chemicals, adhesives and paints and lacquers) is considered for calculation purposes. This result is then compared with a second calculation which is based on the regional background concentrations.

The total daily dose is estimated for the different scenarios from 14.43 µg/kg/bw/d (local scenario) to 0.0534 µg/kg/bw/d (regional background concentration).

Air and drinking water are the most significant routes of uptake, when taking both a local and regional approach to the calculation of the indirect exposure.

4.1.2 Effects assessment

Toxicokinetics, metabolism and distribution

Methyl acetate is absorbed via the lungs in animals and humans, absorption via the oral route is demonstrated. After absorption the substance undergoes hydrolysis to methanol and acetic acid. From the available *in vitro* data it was estimated roughly that the half-life of methyl acetate in blood amounts 2 to 3 hours (rat) and about 2 hours (human). Immediately after stopping a 6-hour inhalation exposure to rats (2,000 ppm (6,040 mg/m^3)) blood concentrations below the limit of quantification (less than 4.6 mg/l) were determined indicating rapid hydrolysis and high clearance of the substance. It appears from these data that the systemic availability of methyl acetate is low.

The main metabolite is methanol which itself is metabolised to formic acid. Formate is introduced into C1-metabolism after activation by reacting with tetrahydrofolate. Humans as

well as monkeys are more sensitive to methanol poisoning compared with rats because of lower tetrahydrofolate content in liver. Therefore interspecies differences in the metabolism were considered mainly of concern at dose levels leading to acute toxicity. Thus rat is a useful model to indicate subacute/subchronic toxic effects below sublethal dosages.

Acute toxicity

Inhalation of methyl acetate causes severe headache and considerable somnolence in humans that need labelling with the EU risk phrase "R 67, Vapours may cause drowsiness and dizziness".

Assessment of the available animal toxicology data indicates that methyl acetate is of low acute toxicity (rats LD_{50} oral: 6,482 mg/kg bw, dermal: >2,000 mg/kg bw, LC_{50} inhalation: >49 mg/l/4h). After oral application and after inhalation of substance vapours, animals showed narcotic symptoms, spasms, dyspnea and vomiting; inhalation of vapours in addition caused irritation of eyes and upper respiratory tract. The substance has narcotic properties if inhaled at concentrations of 34 mg/l (mice) and 56 mg/l (cats) with a short duration of the narcotic action after cessation of exposure.

Irritation

Methyl acetate has proven to cause only weak skin irritation in humans and in rabbits (no oedema, erythema with maximum grade 1 reversible within 48 hours). Eye irritation however, was strong but reversible within 7 days in a Draize eye test with rabbits (with mean scores for observations after 24, 48 and 72 hours of 1/1/1 for iridial irritation and of 2.7/2.3/3 for conjunctival oedema). Exposure to methyl acetate vapours causes irritation to eyes and respiratory tract of humans. Based on these data, the substance has been classified as "Xi (Irritant) " and labelled as "R 36 (Irritating to eyes) ".

Sensitisation

Relevant human data are not available. In a maximisation test with 25 volunteers no sensitisation was observed after exposure to 10% methyl acetate in petrolatum. Taking into account the long experience with human exposure to the substance, and the absence of any reports on contact allergy in exposed persons, methyl acetate is not expected to exhibit skin sensitising properties, especially since the substance is hydrolysed in contact with water by non-specific tissue esterases to methanol and acetic acid. For these substances a skin sensitisation potential is either absent or restricted to a few cases.

Repeated dose toxicity

Reliable experimental animal data on the local and systemic effects after repeated administration of methyl acetate are restricted to the inhalation exposure. After nose-only inhalation during a 28-day treatment period, methyl acetate induced degeneration/necrosis of the rat olfactory mucosa at a concentration of 2,000 ppm on 6 hours/day, 5 days/week (6,040 mg/m^3). There was some concern on minimal effects of systemic toxicity at this concentration (diureses, minimal liver cell dysfunction, adrenal weight increase, and reduced serum cholesterol concentrations). No repeated dose studies on methyl acetate are available for the oral and dermal route. In a non-valid study in cats, inhalation exposure for 5 days to 19-21 mg/l methyl acetate resulted in increased hemoglobin and erythrocyte levels, transient leukocytosis, eye irritation and moderate CNS depression.

There are no adequate data from human experience on repeated or prolonged exposure.

Mutagenicity

Methyl acetate is negative in a bacterial mutation test and a rat bone marrow micronucleus test. Furthermore, the hydrolysis products methanol and acetic acid do not reveal evidence for a mutagenic potential. There is no concern with respect to mutagenicity.

Carcinogenicity

At present no data are known which give relevant concern on carcinogenicity following methyl acetate exposure, although in methanol studies in rats and mice, an increased incidence of lung adenoma/adenomatosis was seen in high-dose male rats only.

Toxicity for reproduction

There are no data available on reproductive toxicity of methyl acetate. However, due to the rapid hydrolysis of this compound it is justified to base hazard assessment with respect to reproduction on the toxicological properties of the immediate metabolites. Concerning the metabolites of methyl acetate, acetic acid appears to be of less significance, since there are no indications of a fetotoxic or teratogenic potential, whereas for methanol some embryo-fetotoxic and teratogenic effects were demonstrated in rodents, however at relatively high concentrations, respectively maternal toxic concentrations only. A NOEC/fertility for methanol of 1,000 ppm (1,300 mg methanol/m^3) was derived from a 2-generation inhalation study in rats. With the assumption that methyl acetate is immediately degraded to methanol at a molar ratio of 1:1, this value can be converted to NOAEC/fertility of about 3,000 mg methyl acetate/m^3. A NOAEC/developmental toxicity for methanol of 1,000 ppm (1,300 mg methanol/m^3) was derived from two studies in mice and rats from intermittent as well as from continuous exposure by inhalation, which can be converted to a NOAEC/developmental toxicity of about 3,000 mg methyl acetate/m^3.

4.1.3 Risk characterisation

4.1.3.1 Workers

Methyl acetate is a liquid with a high-vapour pressure of 217 hPa at 20°C. It is used as a chemical intermediate and as a solvent in different formulations. Exposure routes to be considered at the workplace are inhalation (aerosols and vapour) and skin contact to the liquid methyl acetate.

The toxicological profile of methyl acetate is essentially determined by its local and systemic effects after repeated inhalation, respiratory irritation and developmental toxicity. The following risks at the workplace are considered specifically for each toxicological endpoint. A summary table (**Table 4.2**) containing all scenarios at risk is given at the end of this section.

Acute toxicity

Acute inhalation toxicity

Comparing the lowest LC_{50} value of >24,000 mg/m^3/8 h in mice and the narcotic concentration of 34,000 mg/m^3 in mice with the highest short-term exposure of 2,830 mg/m^3 and the highest shift average value of 768 mg/m^3 (both Scenario 11: flooring works, building trade; without LEV, see **Table 4.1**), there is no concern regarding risks of lethality or narcosis. **Conclusion (ii)**.

Acute dermal toxicity

The occlusive application of 2,000 mg/kg (24 hours) led to no effects in rats. A dose of 140,000 mg/person can be calculated for a human body weight of 70 kg. Comparing this value with the highest dermal exposure estimate of 420-2,100 mg/person (Scenario 11: flooring works) a risk of lethality or other effects is not expected. **Conclusion (ii)**.

Irritation/corrosivity

Acute respiratory tract irritation

Local effects in the respiratory tract with slight to moderate effects in the olfactory epithelium were observed in rats in a 4-week inhalation study. A NOAEC of 1,057 mg/m^3 (350 ppm) and a LOAEC of 6,040 mg/m^3 (2,000 ppm) were determined. In addition information is given on a 5-day inhalation study with a NOAEC of 1,510 mg/m^3 (500 ppm) for nasal effects. Based on the above data methyl acetate can be considered as a respiratory tract irritant. The highest exposure in Scenario 11 (flooring works) with a shift average value of 768 mg/m^3 is considered to be of concern. **Conclusion (iii)**.

Dermal and eyes irritation

Methyl acetate is not classified as irritating to the skin. Liquid methyl acetate is irritating to the eyes of rabbits. Conclusion (ii) is proposed on the grounds that control measures exist which can minimise exposure and risk of irritation. However these must be implemented and complied with to reduce the risk of damage to eyes. **Conclusion (ii)**.

Skin and respiratory sensitisation

Animal data on skin sensitisation are not available. Based on human data and considerations on the metabolism methyl acetate is not expected to exhibit skin sensitising properties. Respiratory sensitisation has not been reported in humans. There is no concern. **Conclusion (ii)**.

Repeated dose toxicity

Inhalation (local effects)

Valid human data on repeated inhalation are not available. The NOAEC for local effects (subacute inhalation study in rats) was determined at 1,057 mg/m^3 (ca. 350 ppm). At the LOAEC of 6,040 mg/m^3 (ca. 2,000 ppm) slight to moderate degeneration and necrosis of the olfactory epithelium was observed. Starting with the experimental NOAEC of 1,057 mg/m^3 (ca. 350 ppm) a 3-fold lower extrapolated chronic NAEC of 350 mg/m^3 (ca. 110 ppm) is estimated. Because the MOS values were considered to be too low (see **Table 4.2**), concern is derived for the following scenarios, 2, 4a/b, 5a/b, 9, 11, and 12. **Conclusion (iii)**.

Inhalation (systemic effects)

In the above-mentioned study a systemic NOAEC of 1,057 mg/m^3 (ca. 350 ppm) was determined. At the LOAEC of 6,040 mg/m^3 (ca. 2,000 ppm) minimal effects of systemic toxicity (diuresis, minimal liver cell dysfunction, adrenal weight increase and reduced serum cholesterol concentrations) were observed. Starting with the experimental NOAEC of 1,057 mg/m^3 (ca. 350 ppm) a 3-fold lower extrapolated chronic NAEC of 350 mg/m^3 (ca. 110 ppm) is estimated. Because the MOS values were considered to be too low (see **Table 4.2**), concern is derived for the following scenarios, 4a/b, 5a/b, 9, and 11. **Conclusion (iii)**.

Dermal (local effects)

Dermal studies with repeated application are not available. Based on the defatting solvent character of methyl acetate, repeated contact can lead to skin dryness or cracking of skin (R 66). Conclusion (ii) is proposed on the grounds that control measures exist which can minimise exposure and risk of irritation. However these must be implemented and complied with to reduce the risk of skin damage. **Conclusion (ii)**.

Dermal (systemic effects)

Dermal studies with repeated application are not available. Thus the subacute inhalation study is taken into account. Considering the minimal degree of systemic toxicity and the fact, that dermal penetration of methyl acetate is lowered by its evaporation from the skin the MOS values were considered to be sufficiently high, concern is not derived. **Conclusion (ii)**.

Combined exposure (systemic effects)

There is no additional scenario, for which concern is raised only due to combined exposure. **Conclusion (ii).**

Mutagenicity

Methyl acetate is negative in a bacterial mutation test and a rat bone marrow micronucleus test. Furthermore, the hydrolysis products methanol and acetic acid do not reveal evidence for a mutagenic potential. There is no concern with respect to mutagenicity. **Conclusion (ii)**.

Carcinogenicity

There are no carcinogenicity studies on methyl acetate. Based on the information that there is no indication for a mutagenic potential methyl acetate is not suspected to be carcinogenic **Conclusion (ii)**.

Toxicity for reproduction (fertility impairment)

A fertility study with methyl acetate is not available. In the subacute inhalation study in rats no effects in the reproductive organs were observed up to the highest tested concentration of 6,040 mg/m^3 (ca. 2,000 ppm). In addition a study with the metabolite methanol is taken into account. A 2-generation-study in rats with continuous exposure showed no effect on reproduction up to the highest tested concentration of 1,000 ppm (ca. 3,000 mg/m^3). A specific effect on fertility is not expected. **Conclusion (ii)**.

Toxicity for reproduction (developmental toxicity)

Inhalation

There are no developmental studies with methyl acetate. Based on kinetic information it is considered to be justified to perform an assessment based on the cleaving products acetic acid and methanol. Concerning acetic acid it is stated that there are no indications for a fetotoxic or teratogenic potential. For methanol a NOAEC of 1,000 ppm for fetotoxicity and 5,000 ppm for maternal toxicity was derived from a developmental study in mice (gestation day 6-15) with intermittent (7 hours) inhalation exposure. The respective NAECs of methyl acetate would be ca. 3,000 mg/m^3 (1,000 ppm) for developmental toxicity and ca. 15,000 mg/m^3 (5,000 ppm) for maternal toxicity. Concern is derived for Scenario 11 (flooring works, building trade) with the highest shift average value of 768 mg/m^3. **Conclusion (iii)**.

The data on human and rodent kinetics indicate that concern should not be expressed for the other scenarios.

Dermal

Based on the above-mentioned study results and the fact, that methyl acetate will evaporate to a certain extent, the MOS values are considered to be high enough to derive no concern. **Conclusion (ii)**.

Combined exposure

There is no additional scenario, for which concern is raised only due to combined exposure. **Conclusion (ii)**.

Conclusions of the occupational risk assessment

The conclusions of the occupational risk assessment are summarised in **Table 4.2**. Exposure scenarios, for which concern is derived are listed in order of exposure extent, beginning with the highest exposure in Scenario 11.

Table 4.2 Conclusions of the occupational risk assessment

Exposure scenario	Inhalation exposure (mg/m^3)	Repeated dose toxicity		Irritation	Developmental toxicity
		local	systemic		
11) Flooring works, building trade	768	**iii**	**iii**	**iii**	**iii**
4) Production of formulations (paints, lacquers, adhesives, cleanser)	294	**iii**	**iii**	ii	ii
9) Pulp and paper production (paints, adhesives)	205	**iii**	**iii**	ii	ii
2) Manufacture and further processing as a chemical intermediate [1)]	31-154	**iii**	ii	ii	ii
5) Metal treatment, electro-engineering, wood treatment	137	**iii**	**iii**	ii	ii
12) Use of cosmetics (nail lacquer remover)	50-130	**iii**	ii	ii	ii

[1)] Companies which did not submit measurement results

4.1.3.2 Consumers

Consumer exposure to methyl acetate may occur via inhalation and dermal route as a result of use of methyl acetate containing products (all-purpose adhesives, carpet adhesives, parquet adhesives, and nail varnish removers). Using a standard "worst-case" scenario for all purpose adhesives consumers may be exposed to an average concentration of 26 mg/m^3 during use (assuming an application time of 60 min) which results in a daily dose of about 1 mg/kg bw/d. The inhalation exposure resulting from use of nail varnish remover has not been forwarded for the risk characterisation because it is considerably lower than that from adhesives. Considering the inhalation exposure resulting from applications of carpet and parquet adhesives considerable higher concentrations have been calculated. However, in view of the infrequent use of these adhesives (once per year) these scenarios have not been forwarded for the risk characterisation.

Oral exposure to methyl acetate will occur due to its presence in food as a natural flavouring substance as well as from consumption of sugar produced from molasses and from use as an extraction solvent for caffeine, irritating substances, etc. The oral exposure from food was estimated to be in the range of 1-10 mg/kg bw/d.

Repeated dose toxicity

Local olfactory effects due to inhalation

During application of all-purpose adhesives the consumer may be exposed to a concentration of 26 mg/m^3 methyl acetate for a contact time of 60 minutes. Methyl acetate induced degeneration/necrosis of the rat olfactory mucosa at a concentration of 6,040 mg/m^3 after nose-only inhalation during a 28-day treatment period. The margin of safety for local effects between the exposure level and the NOAEC for effects on the mucosa of 1,057 mg/m^3 is judged to be sufficient because a worst-case exposure scenario was taken into account and the high LOAEC of 6,040 mg/m^3 (no steep dose-response-relationship). There is a large distance between the high and the mid concentration of methyl acetate in the HMR study used for derivation of the NOAEC. It could be that the NOAEC might be higher if an additional dose would have been tested. **Conclusion (ii)**.

Inhalation exposure - Systemic effects

In repeated dose toxicity studies in rats (28-day inhalation) the NOAEC for systemic effects was 1.057 mg/l which can be converted to a NOAEL of 304 mg/kg bw/d estimating the inhaled amount of the substance using the respiratory minute volume 0.8 l/min/kg and exposure duration of 360 min/day. The margin of safety between the exposure estimate of about 1 mg/kg bw/d and the NOAEL is judged to be sufficient taking in account all assumptions being applied in the exposure estimations. **Conclusion (ii)**.

Oral exposure

The NOAEL for systemic effects of 304 mg/kg bw/d was converted from the NOAEC of a 28-day inhalation study. The margin of safety between the oral uptake of up to 10 mg/kg bw/d and the NOAEL is judged to be sufficient taking in account all uncertainties of the exposure estimations. Thus, the substance is of no concern in relation to consumer exposure. **Conclusion (ii)**.

Toxicity for reproduction

There are no data available on the reproductive toxicity of methyl acetate itself. However, due to the rapid hydrolysis of the substance the effect assessment with respect to reproduction can be based on the toxicological properties of the immediate metabolites. For acetic acid there are no indications of a fetotoxic or teratogenic potential, whereas for methanol embryo-fetotoxic and teratogenic effects were demonstrated in rodents at relatively high concentrations, respectively maternal toxic concentrations. With methanol a value of 1,300 mg/m^3 was derived for the NOEC/fertility as well as for the NOAEC/developmental toxicity. Under the assumption that methyl acetate is immediately degraded to methanol at a molar ratio of 1:1, this value can be converted to NOAEC/fertility as well as NOAEC/developmental toxicity of about 3,000 mg methyl acetate/m^3.

The margin of safety between the calculated inhalation exposure of 26 mg/m^3 and the NOAEC for fertility and developmental toxicity of 3,000 mg/m^3 obtained by conversion from methanol data is judged to be sufficient. Species differences in the metabolism of formate due

to lower tetrahydrofolate content in the liver of primates have to be taken into account, however, at the low exposure conditions there should be no concern to consumer exposure. **Conclusion (ii)**.

4.1.3.3 Humans exposed via the environment

Indirect exposure to methyl acetate via the environment occurs mainly by air and drinking water. $PECs_{air}$ of 0.035 mg/m^3 and 0.00013 mg/m^3 have been calculated for the local and the regional scenario, respectively. For the local scenario an intake of a total daily dose of 0.0144 mg/kg bw/d is calculated (as a worst case), whereas for the regional scenario the respective figure is smaller (0.0534 µg/kg bw/d).

Repeated dose toxicity

Local olfactory effects due to inhalation

The margin of safety for local effects between the local exposure level of 0.035 mg/m^3 as well as the even 100-fold lower regional level and the NOAEC for effects on the mucosa of 1,057 mg/m^3 observed in a 28-day inhalation study in rats is judged to be sufficient. Thus, the substance is of no concern in relation to indirect exposure via the environment. **Conclusion (ii)**.

Inhalation exposure - Systemic effects

For the risk characterisation the total daily intake for the local and the regional scenario is compared with an oral NOAEL for systemic effects of 304 mg/kg bw/d which was converted from the NOAEC of a repeated dose toxicity studies in rats (28-day inhalation, NOAEC 1,057 mg/m^3). The margins of safety expressed by the magnitude between the calculated daily intakes and the NOAEL are considered to be sufficient for both scenarios. Thus, the substance is of no concern in relation to indirect exposure via the environment. **Conclusion (ii)**.

Toxicity for reproduction

There are no data available on the reproductive toxicity potential of methyl acetate itself. However, due to the rapid hydrolysis of the substance the effect assessment with respect to reproduction can be based on the toxicological properties of the immediate metabolites acetic acid and methanol. Due to the even lower exposure via the environment as compared to the direct exposure there is no concern. The margin of safety is considered to be sufficient, too. Thus, the substance is of no concern in relation to indirect exposure via the environment. **Conclusion (ii)**.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

Explosive properties and oxidising properties of methyl acetate are not considered to form a hazard. Since methyl 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. **Conclusion (ii)**.

5 RESULTS

5.1 ENVIRONMENT

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

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 because of concern after inhalation for the following endpoints: irritation, local and systemic effects after repeated exposure, and developmental toxicity.

Consumers

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