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ETHYL ACETOACETATE

CAS No: 141-97-9

EINECS No: 205-516-1

Summary Risk Assessment Report

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SUMMARY RISK ASSESSMENT REPORT

2002

Germany

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PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substance ethyl acetoacetate 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 original risk assessment report that can be obtained from the European Chemicals Bureau[1]. The present summary report should preferably not be used for citation purposes.

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

CONTENTS

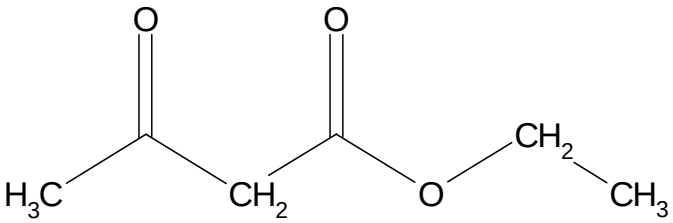
TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS Number: 141-97-9
EINECS Number: 205-516-1
IUPAC Name: Ethyl acetoacetate
Synonyma: 1-Ethoxybutane-1,3-dione
3-Oxobutanoic acid ethylester
Acetessigsäureethylester
Aceto acetato de etilo
Acétoacétate de l'éthyle
Acetoacetic acid, ethyl ester
Butanoic acid, 3-oxo-, ethylester
Butansäure, 3-oxo-, ethylester
Ethylacetoacetat
Ethyl acetoacetate
3-Oxobutansäureethylester
EAA
Ethyl 3-oxobutanoate
Ethyl acetonecarboxylate
Ethyl acetylacetate
Empirical formula: $C_6H_{10}O_3$

Structural formula:



Molecular weight: 130.14 g/mol

1.2 PURITY/IMPURITIES, ADDITIVES

Purity: ≥ 99.0% w/w
Impurity: < 0.5% w/w ethanol
< 0.1% w/w water
<= 0.15% w/w ethyl acetate
<= 0.12% w/w acetone
<= 0.1% w/w methyl acetoacetate
<= 0.1% w/w 3-acetyloxy-2-butenoic acid ethylester
< 0.05% w/w acetic acid
Additives: none

1.3 PHYSICO-CHEMICAL PROPERTIES

Table 1.1 Summary of physico-chemical properties

Property	Value	Reference
Melting point	-44 - -39°C [1)] - 39°C	Hoechst (1994a) CRC (1991/92)
Boiling point	178 - 187°C	Hoechst (1994a)
Density	1.0325 g/cm^3 at 15°C [2)] 1.0368 g/cm^3 (at 10°C relative to water at 4°C)	Hoechst (1994a) CRC (1991/92)
Vapour pressure	1 hPa at 20°C [3)] 1.3 hPa at 28.5°C	Hoechst (1994a) CRC (1991/92)
Surface tension	62.6 mN/m at 20°C (conc: 1.002 g/l)	Hoechst (1996c) (experimental, Annex V of Directive 92/69/EEC, A.5)
Partition coefficient	logK_{ow} 0.25	Catz & Friend (1989)
Water solubility	125 g/l at 16°C	Hoechst (1994a)
Flash point	65°C	CHEMSAFE
Autoflammability	350°C	CHEMSAFE (experimental according to DIN 51794)
Flammability	not flammable	
Explosive properties	not explosive	structural reasons
Oxidizing properties	not oxidizing	structural reasons
Conversion factors	1 ppm ≅ 5.4 mg/m^3	

[1)] Melting point: in accordance with the literature value, the freezing point given in the safety data sheet was determined to be in the range of -44 and -39 °C.

[2)] Density: The value given in the safety data sheet was confirmed by the literature value.

[3)] Vapour pressure: The value given in the safety data sheet was confirmed by the literature value. The vapour pressure of 1 hPa at 20 °C was used for the calculations in the Risk Assessment Report.

1.4 CLASSIFICATION

Classification according to Annex I of Directive 67/548/EC: Not classified[2].

In Germany ethyl acetoacetate is classified according to water-hazard class 1 (slightly hazardous to water).

[2] Based on the information available, no classification of the substance is possible, following the criteria set out in Annex VI of Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (OJ B 196, 1.08.1967 p.1).

2 GENERAL INFORMATION ON EXPOSURE

According to information provided in the available IUCLID data sets there are four producers (> 1,000 t/a) of ethyl acetoacetate within the EU. The production volume of each company is between 1,000 and 5,000 t/a. Two of these companies discontinued their production in the territory of the EU in the years 1993 and 1994 respectively. There is no information on possible exports or imports.

Ethyl acetoacetate is essentially used as an intermediate in the production of pharmaceuticals, plant protection products as well as dyes and pigments. Smaller quantities of the substance are used as fragrance and odour agent. Further possible uses of the substance include employment as a solvent in the paint industry, in cosmetic products such as nail varnish and in the household. It is also described that the substance may be used as a paper impregnating agent and in the coating of paper, as a hardening accelerator for polyester paints, as an additive in the production of resin and in the production of colour films. In aromatic substances identical to those which naturally occur, ethyl acetoacetate may be included in milk products, confectionery, cakes and pastries etc.

According to information provided by the two companies which currently manufacture ethyl acetoacetate, 94.6 % of the substance is used as an intermediate for plant protection products, pharmaceuticals, stabilizers, additives, catalysts and other products. 3.8% are employed as fragrant or odour agent with a wide range of uses (e.g. household chemicals) and 1% is used as a solvent in paints and lacquers. The area of use of the remaining quantity of the substance amounting to 0.6% is not clear.

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

Release of ethyl acetoacetate into the environment during production is expected to occur to only a very small extent since production takes place wastewater free and in a closed system and the exhaust gas is drawn off for combustion. Low-level releases into the environment are only expected during cleaning and maintenance work as well as during filling operations. Releases into the wastewater and into the exhaust air are expected during further processing and use of the substance.

No information is available on the remainder content of ethyl acetoacetate in the sequence products.

The environmental behaviour of ethyl acetoacetate is determined by the following characteristics:

- the estimated atmospheric half-life is approximately 10.3 days,
- ethyl acetoacetate is readily biodegradable,
- evaporation from surface water is not an important fate process,
- the average K_p value indicates no relevant adsorption onto sediment or soil.

Based on the physico-chemical properties of ethyl acetoacetate, the hydrosphere is the preferred target compartment and neither relevant bioaccumulation nor geoaccumulation is expected. In waste water treatment plants (WWTPs) 87.4% of the substance are estimated to be removed predominantly by biodegradation.

Predicted Environmental Concentrations (PECs) are calculated for the local aquatic 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 concentrations are in the range of 1.45 to 1.7 µg/l.

Ethyl acetoacetate is also used as an odour agent in household chemicals, solvent in paints and lacquers and in paper coating and paper impregnation. Default calculations according to the TGD for the formulation and processing of the different products and for paper recycling gives PECs in the range of 2.95 to 126 µg/l.

No monitoring data in the aquatic environment are available.

For the sediment compartment no PEC-estimation is performed, because relevant adsorption of ethyl acetoacetate onto sediment is not expected.

Release into the atmosphere during production of ethyl acetoacetate at one company is given as 29 kg/a. No further information with regard to release into the atmosphere during production and processing or use of the substance is available. No releases of the substance into the atmosphere are to be expected during paper recycling.

Taking into account the exposure tables in Annex 1 of the TGD, the releases into the atmosphere and the resultant local concentrations in air can be calculated on the basis of the physico-chemical properties of the substance and the quantities of the substance involved in production, processing and use. Based on this data air concentrations in the range of 0.03 to 1.4 µg/m^3 are calculated.

The release of ethyl acetoacetate to soil is expected to occur through atmospheric deposition after local release to the atmosphere. The input through sludge application on agricultural soil is considered negligible, as ethyl acetoacetate does not partition to a significant extent to sewage sludge in the WWTP.

From the total annual deposition in the vicinity of the generic site the maximum equilibrium concentration in soil is calculated according to the procedure proposed in the TGD. The resulting bulk concentration in soil (natural soil and agricultural soil) is 0.04 µg/kg wwt, the respective porewater concentration is 0.1 µg/l.

The regional background concentrations calculated according to the SimpleBox model are low and do not contribute to a significant extent to the local concentrations. The values are:

$PECregional_{aquatic}$ = 0.04 µg/l
$PECregional_{air}$ = 0.37 ng/m^3
$PECregional_{agr.soil}$ = 1.8 ng/kg

3.2 EFFECTS ASSESSMENT

Only a few valid data on ecotoxicological effects of ethyl acetoacetate exist, which are listed in **Table 3.1**.

Table 3.1 Ecotoxicological effect data of ethyl acetoacetate

Species	Effect concentration	Reference
Leuciscus idus	48h LC_{50} = 275 mg/l 48h LC_{50} = 515 mg/l	Juhnke, Lüdemann 1978
Daphnia magna	24h EC_{50} = 790 mg/l	Bringmann, Kühn 1977
Daphnia magna	24h EC_{50} = 800 mg/l	Bringmann, Kühn 1982
Scenedesmus subspicatus	72h EC_{50} > 500 mg/l 72h EC_{10} > 500 mg/l	Hoechst 1996b
Scenedesmus quadricauda	8d EC_3 = 7.6 mg/l	Bringmann, Kühn 1978, 1980a
Microcystis aeruginosa	8d EC_3 = 90 mg/l	Bringmann, Kühn 1976, 1978

Long-term toxicity tests with fish and invertebrates are not available.

For the determination of the Predicted No Effect Concentration (PNEC) the 48h-LC_{50} of 275 mg/l is regarded as a valid acute studies for aquatic species, according to the TGD. An assessment factor of 1,000 is proposed for a data basis like the one available for ethyl acetoacetate and a $PNEC_{aqua}$ of 275 µg/l is derived.

The toxic threshold concentrations (EC_5-values) for different species of protozoa were derived in cell multiplication inhibition tests showing less sensitivity than for *Pseudomonas putida*, which was assessed in a cell multiplication inhibition test as well.

According to the TGD, *Pseudomonas* test must be numbered among the more sensitive tests and an assessment factor of 1 has to be applied. Accordingly, the $PNEC_{microorganisms}$ is set at 33 mg/l.

There are no experimental results with benthic organisms available and there is no need for performing an indicative quantitative risk assessment for the sediment compartment, because ethyl acetoacetate shows no relevant adsorption and there are no monitoring data on ethyl acetoacetate -concentrations in sediment available

It is not possible to derive a PNEC for the atmospheric compartment due to the lack of experimental data.

Data on effects to terrestrial organisms are not available. In an indicative risk assessment for the soil compartment, the aquatic PNEC of 275 µg/l can be used and compared to the concentration in soil pore water.

3.3 RISK CHARACTERISATION

The possible risks to microorganisms in waste water treatment plants are evaluated for municipal and industrial facilities. For all considered scenarios the PEC/PNEC ratios are below one and a risk for the function of the WWTPs is not expected.

For surface water a comparison between PEC and PNEC for all relevant exposure scenarios is performed. For all considered scenarios the PEC/PNEC ratios are below one and a risk for the aquatic environment is not expected.

From the current manufacturing and use of ethyl acetoacetate no risk for the sediment compartment is expected.

Due to the fast atmospheric photooxidation and the low resulting concentrations in air, adverse effects on organisms and abiotic effects upon the atmosphere, like global warming and ozone depletion are not expected from ethyl acetoacetate.

From an indicative risk assessment for the soil compartment no risk is deduced for the present data configuration and there is no need for further testing and/or gathering of exposure information.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure

4.1.1.1 Occupational Exposure

Ethyl acetoacetate is primarily used as a chemical intermediate for the manufacture of pharmaceuticals, pesticides, dyes and pigments. Apart from these uses, approximately 5 % of the total produced quantity is employed:

- directly or in perfume oils (in concentrations up to 5 %) as fragrance or odorant (for e.g. body care products, detergents and sanitary cleaning products, room deodorants),
- as a flavouring substance in foodstuffs,
- as a solvent for cosmetics (particularly for nail varnish),
- as an additive in resin manufacture,
- as a hardening accelerator in polyester paints,
- for impregnating and coating of paper,
- in the manufacture of colour films.

Occupational exposure limits for ethyl acetoacetate are not known.

According to the above listed uses of ethyl acetoacetate, occupational exposure scenarios are considered for chemical industry, the industrial area and the skilled trade.

With regard to inhalation exposure, exposure to ethyl acetoacetate in vapour form and, in case of spray painting, to aerosols have to be considered here. The assessment of inhalation exposure is based on measured data, expert judgement and estimates according to the EASE model.

As regards dermal exposure, only limited information on the suitability of the personal protective equipment (here gloves) is available. Furthermore, for most exposure scenarios, the regular use of gloves cannot be presupposed for the exposure assessment. Therefore, dermal exposure is assessed for the unprotected worker. The limited protection of unsuitable gloves cannot be considered.

The results for the different scenarios are summarised in **Table 4.1**. In part, model estimates and exposure levels based on measurement results are given.

Table 4.1 Summary of exposure data

Exposure scenario	Duration and frequency	Inhalation exposure Shift average [mg/m³]	Dermal exposure Shift average [mg/p/day]
Chemical industry			
Manufacturing (liquid) and further processing as a chemical intermediate (pharmaceuticals, pesticides, dyes and pigments)	shift length, daily	< 2.5 [1] (with LEV)	42 – 420 [2]
Manufacture of cosmetics (specially nail varnish, after-shave lotion)	shift length, daily	< 2.5 [1] (with LEV)	42 – 420 [2]
Industrial area			
Use of perfume oils (content < 5 %) in the manufacture of cleaning products (content < 1 %) and air deodorants (content < 1.25 %)	batch processing 2 hours, daily	0.75 – 4 [2] (with LEV) 14 - 68 [2] without LEV)	2 – 21 [2]
Manufacture of polyester paints, use as an additive in resins and as hardening accelerator (formulation companies)	batch processing 2 hours, daily	< 6 [3] 0.75 - 4 [2] (with LEV) 14 – 68 [2] (without LEV)	42 – 420 [2]
Manufacturing of foodstuffs and colour films, clustered because of comparable standards of cleanliness	shift length, daily	3 –16 [2] (with LEV)	42 – 420 [2]
Use as an additive in formulations, for impregnating and coating of paper, assumption: content 5 %	shift length, daily	17.5 [3] (90th percentile)	2 – 21 [2]
Use as a hardening accelerator in polyester paints during spray painting (content 1 - 5 %)	shift length, daily	app. 20 [3] 27 – 54 [2]	6 – 65 [2]
Skilled trade			
Use as hardening accelerator in polyester paints for repair lacquering during spray painting (content 1 - 5 %)	assumed 2 hours, daily	33.5 – 67 [2]	65 – 325 [2]
Use of cleansers (all-purpose cleanser, washing detergents) content: 0.05 %	shorter than shift length, daily	0 – 0.6 [2]	3 – 10 [2]
Short term use of cosmetics content, assumed content 1 %,			
- nail - lacquers (occasional use)	occasional	low [4]	low [4]
- after - shave lotion (daily use)	daily	low [4]	5 – 26 [2]

[1] Exposure assessment based on measurement data
[2] Exposure assessment based on model estimates (EASE model)
[3] Exposure assessment based on analogous data form 2-ethoxyethylacetate
[4] Exposure assessment based on expert judgement

4.1.1.2 Consumer Exposure

In the main fields of use, ethyl acetoacetate is almost exclusively used as an intermediate and is therefore no longer present in the final products. However, a residual exposure cannot be excluded by use of a few consumer products. In some products, it may be used as a fla-vouring substance (in concentrations of <10 ppm in milk products, confectionery and bakery products) and as an odorant in perfume oils in concentrations of up to 5 %. Perfume oils are used in various products (e.g. body care products, detergents and sanitary cleaning products, room deodorants).

Dermal exposure to cosmetics

Assuming the use of 0.75 g of Eau de Cologne, which contains 5 % perfume oil consisting of 5 % odorant, 5 times a day, an exposure of the consumer to approximately 9 mg odorant per day will result (corresponding to 100 – 1,000 µg range/kg bw/d).

Assuming the use of 5 drops of Eau de Perfume, which contains 15 % perfume oil consisting of 5 % odorant, per day, an exposure of the consumer in the 10 - 100 µg range/kg bw/d will result.

The use of body lotion applied in a quantity of 16 g lotion/day will result in an exposure of the consumer to the odorant in the range of 100 - 1000 µg/kg bw/d.

Creams and ointments contain less than 1 % perfume oil consisting of 5 % odorant. When 0.8 g face cream is used per day, dermal exposure of the consumer to the odorant will amount to about 10 µg/kg bw/d.

Inhalation exposure to all-purpose cleaners, detergents, and room deodorants

Inhalation exposure of the consumer to the odorant is in the range of 10 - 100 µg/kg bw/d when a fluid all-purpose cleaner is used with a content of perfume oil of 12 % (of which 5 % accounts for odorant) and application under standard conditions is assumed.

Using a detergent under standard conditions in the washing machine (20 % perfume oil containing 5 % odorant), an inhalation exposure of the consumer will amount up to 1,000 µg odorant/kg bw/d.

Using a solid room deodorant (25 % perfume oil containing 5 % odorant) under standard conditions, the exposure to the odorant will be in the range of 1 -10 µg/kg bw/d.

Summary

Taking into account that ethyl acetoacetate is no longer present in most consumer products, the combined exposure of the consumer may be in the range of 100-1,000 µg/kg bw/d.

4.1.1.3 Humans exposed via the Environment

Indirect exposure via the environment is calculated using data for intake via drinking water, food and air. An intake of a total daily dose of 0.787 µg/kg bw is calculated for the local scenario and of 0.00141 µg/kg bw for the regional scenario.

4.1.2 Effects Assessment

Absorption of ethyl acetoacetate via the oral route is demonstrated in animals, absorption via the lungs can be assumed. It can be anticipated that ethyl acetoacetate is partially cleaved already in the gastrointestinal tract due to acidic pH values or by bacterial activity. The absorbed portion of ethyl acetoacetate will be hydrolysed into 3-oxobutanoic acid and ethanol by the unspecific esterases of the blood. The acid moiety forms an endogenous constituent within the lipid metabolism and is further metabolized predominantly to carbon dioxide and water; ethanol will be metabolized on known pathways. In general esterase activities in human plasma are far lower than in the plasma of rats. Therefore it is to anticipate, that the stability (half-life) of systemically available ethyl acetoacetate is higher in humans than in rats. The main route of elimination of ethyl acetoacetate and/or its metabolites is urinary excretion or exhalation of the metabolic product carbon dioxide in the breath.

Human data on acute toxicity caused by ethyl acetoacetate are not available. Ethyl acetoacetate has shown low toxicity after oral application with LD50s for rats in the range of 3,980-12,300 mg/kg bw. There are no valid data available on toxicity by inhalation. However, the inhalation toxicity seems to be low as judged on the basis of a poorly reported test with rats surviving an 8-hour exposure to saturated substance vapours. Acute dermal toxicity in the rabbit is low, the dermal LD50 value was determined to 10 ml/kg bw (10,300 mg/kg bw).

Human data on local irritant properties of ethyl acetoacetate are not available. Ethyl acetoacetate exhibits mild irritating properties to the skin and eyes of rabbits, depending on the duration of exposure and the dose. It is concluded that the substance does not have local corrosive properties.

Valid human or animal data on sensitization are not available. In an human maximization test 26 volunteers did not show any positive skin reactions after topical challenge treatment with 8 % ethyl acetoacetate 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, ethyl acetoacetate is not supposed to exhibit skin sensitizing properties.

There is no information on health effects in humans following repeated exposure to ethyl acetoacetate via any route. Following repeated oral exposure of the substance in 28-day studies to rats, no treatment-related adverse effects (including haematology, clinical chemistry, gross necropsy and histopathology) were reported up to doses of 1,000 mg/kg bw/d (NOAEL).

Ethyl acetoacetate showed negative results in a bacterial mutation test and in *in vitro* chromosomal aberration tests. There is no concern with respect to mutagenicity.

There are no data on cancerogenicity of ethyl acetoacetate. From experience on other comparable compounds in combination with the knowledge on the metabolites there is no reason to assume a concern regarding cancerogenic effects of the substance.

There are no human data available on the reproductive toxicity of ethyl acetoacetate. The potential to adversely affect reproduction and development was investigated at a screening level in a study according to OECD-Guideline 421 with oral administration to rats. No statistically relevant effects were observed at doses up to and including 1,000 mg/kg bw/d taking into account historical control data from 7 other studies according to OECD-Guideline 421. Hence, from the results of the current study a NOAEL for reproductive toxicity of 1,000 mg/kg bw/d has been estimated.

4.1.3 Risk Characterisation

4.1.3.1 Workers

For the purpose of risk characterisation, it is assumed that inhalation of vapour and skin exposure are the main routes of exposure. Oral exposure is not considered to be a significant route of exposure under normal working practices.

The acute inhalation toxicity in rats appears to be low. No lethality occurred at saturated vapour conditions with an estimated exposure concentration of 1,000 ml/m^3 (1 hPa, 20 °C). The highest exposure level reported is 13 ml/m³ (68 mg/m³) in the industrial area. This exposure lies far below 1,000 ml/m^3. During normal use acute inhalation risks are not considered of concern **(conclusion ii)**.

The dermal LD_{50} for rats is > 10,000 mg/kg. This value is much higher than the calculated highest dermal exposure of 6 mg/kg (calculated on the basis of 1 mg/cm^2, exposed skin area 420 cm^2, 70 kg bodyweight). This level of exposure is calculated for the chemical industry and some industrial applications (without PPE). Therefore acute dermal risks are not considered of concern **(conclusion ii)**.

Ethyl acetoacetate is not suspected to be a respiratory tract irritant. Inhalation exposure of workers is therefore not anticipated to result in relevant respiratory tract irritation **(conclusion ii)**.

Ethyl acetoacetate is not classified as "irritating" to skin or eyes. Dermal contact at workplaces is therefore not anticipated to result in relevant local damage **(conclusion ii)**. Although data are not sufficient to allow a definite assessment of chronic local effects, the conclusion of no concern is considered justified for repeated dermal contact too.

Ethyl acetoacetate is not supposed to be a skin sensitizer. Dermal contact at workplaces is therefore not anticipated to result in skin sensitization **(conclusion ii)**. There are no experimental data available on respiratory sensitization. According to the fact, that during all the years of use no notice of specific case reports has been given, inhalation exposure is not suspected to result in respiratory tract sensitization **(conclusion ii)**.

Inhalation studies with repeated administration are not available. The systemic toxicity of ethyl acetoacetate is judged on the basis of the available oral 28-day studies in rats. In these studies, no adverse effects were observed at the highest tested oral dose of 1,000 mg/kg/d. Taking into account a possible chronic threshold level lower than the experimental NOAEL of the subacute rat study, equivalent absorption by the oral and inhalation route, metabolic rate scaling, biotransformation of the carboxylic ester to acetoacetic acid and ethanol (see comprehensive risk assessment report), it is assumed that the anticipated human NAEC for chronic inhalation exposure might be between 100 ml/m^3 and 1,000 ml/m^3 (about 500 mg/m³ to 5,000 mg/m³). Comparison of the available toxicological information on repeated dose toxicity with the highest shift average value of 68 mg/m³ (industrial area and skilled trade) is not considered to result in repeated dose toxicity by inhalation **(conclusion ii)**.

Comparison of the experimental results of the oral 28-day studies in rats (no toxic effects at the highest tested dose of 1,000 mg/kg/d) with the highest repeated dermal exposure of 420 mg/p/d (highest level in industry, without PPE) suggests that systemic health risks due to repeated dermal exposure are not expected (for details see comprehensive risk assessment report; (**conclusion ii**). Systemic health risks due to combined exposure are not considered of concern **(conclusion ii)**.

According to negative base set tests there is no concern for ethyl acetoacetate with respect to mutagenicity **(conclusion ii)**. There are no carcinogenicity data available. Ethyl acetoacetate is not suspected to be a carcinogen **(conclusion ii)**.

From an oral reproductive toxicity screening test (OECD 421) a NOAEL of 1,000 mg/kg/d is obtained. Taking into account historical control data, effects observed at the highest dose level of 1,000 mg/kg/d are not considered treatment-related. Thus, ethyl acetoacetate is not considered to be a reproductive toxicant. The highest shift average values are reported to be 68 mg/m³ (industrial area and skilled trade) for inhalation exposure and 420 mg/person/day for dermal contact. Dermal contact is not considered to be of concern **(conclusion ii)**. **Conclusion ii** seems to be appropriate for all inhalation exposure scenarios as well. However, because the assessment of reproduction toxicity is based on a screening test with its intrinsic statistical limitations, possible toxicological consequences due to inhalation exposure levels higher than reported cannot be assessed with sufficient certainty.

4.1.3.2 Consumers

Consumer exposure may occur as a result of using cosmetics and household products. The combined exposure to the odorant in these products results in a predicted exposure range of 100 – 1,000 µg/kg bw/d. Although the calculated sum of all estimated possible exposures is higher than this range it seems unlikely that the real exposure of consumers will exceed this range.

Repeated dose toxicity

Two studies in rats have shown no relevant treatment-related effects associated with repeated oral administration. A NOAEL of 1,000 mg/kg bw/d was derived. Following the exposure assessment consumers may be exposed dermally and via inhalation to ethyl acetoacetate. The NOAEL of 1,000 mg/kg bw/d was derived from oral 28-day studies on rats. The margin of safety is judged to be sufficient, even if interspecies differences in esterase activities and route-to-route extrapolation are taken into consideration **(conclusion ii)**.

Reproductive Toxicity

Data from a screening study according to OECD-Guideline 421 with oral administration to rats did not give evidence for adverse effects up to 1,000 mg/kg bw/day. A NOAEL for reproductive toxicity of 1,000 mg/kg bw/day was estimated. Taking into account the estimated low exposure in the range of 100 – 1,000 µg/kg bw/d it can be concluded that there is no concern **(conclusion ii)**.

4.1.3.3 Humans exposed via the environment

Indirect exposure via the environment is calculated using data for intake via drinking water, food and air. An intake of a total daily dose of 0.787 µg/kg bw is calculated for the local scenario and 0.00141 µg/kg bw for the regional scenario.

Repeated dose toxicity

The main route of exposure is the drinking water (about 80 %). For the risk characterization the total daily intake for the local and the regional scenario is compared with an oral NOAEL of 1,000 mg/kg bw/d which was derived from a 28-day rat study. The margins of safety expressed

by the magnitude between the calculated exposure values 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)**.

Reproductive Toxicity

From the results of an OECD-Guideline 421 study with oral application to rats a NOAEL for reproductive toxicity of 1,000 mg/kg bw/d was estimated. Taking into account the low exposure it can be concluded that the margin of safety for both the local and the regional scenario is considered to be sufficient. Thus, there is no concern in relation to indirect exposure via the environment **(conclusion ii)**.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

In view of its chemical structure, ethyl acetoacetate is not expected to have an oxidizing potential. The substance is neither explosive nor flammable. Therefore with regard to the physico-chemical properties and with regard to the occupational exposure and the consumer exposure, ethyl acetoacetate is not expected to cause specific concern relevant to human health.

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 RESULTS

5.1 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.

This conclusion applies to all environmental spheres regarded for the production, processing, formulation and use of ethyl acetoacetate.

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

Workers

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.

Irrespective of conclusion ii for workers for all exposure scenarios and toxicological endpoints information should be given that health effects at inhalation exposure levels exceeding those documented in the report cannot be assessed with sufficient certainty.

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)

Given the physico-chemical data, ethyl acetoacetate is considered not to form a risk with respect to flammability, explosive properties, and oxidising properties (**conclusion ii**).

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.