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TOXICOLOGICAL EVALUATIONS

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TOXICOLOGICAL EVALUATION

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Acetoacetic acid ethyl ester

No. 246

CAS No. 141-97-9

BG Chemie
Berufsgenossenschaft der chemischen Industrie

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Acetoacetic acid ethyl ester

This Toxicological Evaluation replaces the previously published version in volume 7.

1 Summary and assessment

The available data on the toxicokinetics and metabolism of acetoacetic acid ethyl ester are scanty. It is assumed, however, that the ester is absorbed by the body, then hydrolysed to a considerable extent by esterases to acetoacetic acid and ethanol and finally metabolised to CO_2 and water. Toxic effects are likely to be due to the uncleaved ester, if anything, or to very high doses of the substance, as the amounts of ethanol resulting from ester hydrolysis under conditions of moderate exposure to acetoacetic acid ethyl ester are far below the toxic levels for ethanol. Acetoacetic acid is a natural intermediate of normal fatty acid catabolism and therefore cannot be considered to be of toxicological relevance.

Hence, acetoacetic acid ethyl ester is of low toxicity in animals following single oral, dermal and inhalation administration (LD_{50} rat oral 3980 to 12000 mg/kg body weight; LD_{50} mouse oral 3200 to 6400 mg/kg body weight; LD_{50} rabbit dermal > 10300 mg/kg body weight; LD_{50} guinea pig dermal > 20 ml/kg body weight; LC_{50} rat (6 hours) > 1129 ppm (equivalent to 5995 mg/m³)). No specific signs of toxicity were observed.

In two studies in rats, 4-week oral administration of acetoacetic acid ethyl ester caused no treatment-related effects up to the highest test dose of 1000 mg/kg body weight.

Depending on the duration of exposure and dosage, acetoacetic acid ethyl ester is not irritant to slightly irritating to the skin, and slightly irritating to the eye. There are no reports of sensitising effects of the substance on the skin of guinea pigs and humans. The available findings, however, are insufficiently documented, and in one case the result is of little significance.

In the Salmonella/microsome assay, acetoacetic acid ethyl ester is not mutagenic. In an in vitro study, which had methodological limitations, no chromosome-damaging potential was detected. In contrast, two tests in *Esche-*

richia coli have given contradictory results with respect to the mutagenic potential of the substance. Two DNA repair tests using *Bacillus subtilis* have also produced contradictory findings as regards the DNA-damaging potential of acetoacetic acid ethyl ester. In *Saccharomyces cerevisiae*, acetoacetic acid ethyl ester fails to induce mitotic recombinations. The studies conducted so far support the assessment that acetoacetic acid ethyl ester is devoid of any relevant genotoxic potential.

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area ("MAK-Kommission") of the Deutsche Forschungsgemeinschaft will investigate the possibility of establishing a MAK value for the chemical.

2 Name of substance

2.1	Usual name	Acetoacetic acid ethyl ester
2.2	IUPAC name	3-Oxobutanoic acid ethyl ester
2.3	CAS No.	141-97-9
2.4	EINECS No.	205-516-1

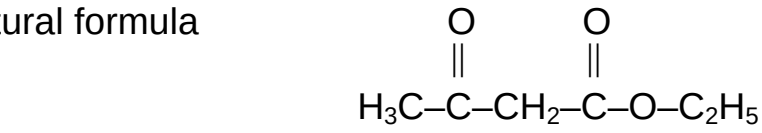
3 Synonyms, common and trade names

Acetessigester
Acetessigsäureethylester
Acetoacetic acid ethyl ester
Acetoacetic ester
Acetylessigsäureethylester
Active acetyl acetate
Active acetylacetate
Butanoic acid, 3-oxo-, ethyl ester
Diacetic ester
EAA
1-Ethoxybutane-1,3-dione
Ethyl acetoacetate
Ethyl acetonecarboxylate
Ethyl acetyl acetate

Ethyl acetylacetate
Ethyl acetyl acetonate
Ethyl beta-ketobutyrate
Ethyl 3-oxobutanoate
Ethyl 3-oxobutyrate
Ethylacetacetat
Ethylacetoacetat
Ethylacetylacetat
β-Ketobuttersäureethylester
3-Oxobutansäureethylester

4 Structural and molecular formulae

4.1 Structural formula



4.2 Molecular formula $C_6H_{10}O_3$

5 Physical and chemical properties

5.1	Molecular mass, g/mol	130.14	
5.2	Melting point, °C	–44 to –39	(Hoechst, 1994)
		–45	(Lide and Frederikse, 1996)
5.3	Boiling point, °C	178–187 (at 1013 hPa)	(Hoechst, 1994)
		180.8	(Lide and Frederikse, 1996)
5.4	Vapour pressure, hPa	1 (at 20 °C)	(Hoechst, 1994)
5.5	Density, g/cm³	1.0368 (at 10 °C)	(Lide and Frederikse, 1996)
		1.0325 (at 15 °C)	
		0.9958 (at 50 °C)	(Hoechst, 1994)
5.6	Solubility in water	125 g/l (at 16 °C)	(Hoechst, 1994)
5.7	Solubility in organic solvents	Soluble in benzene, miscible with ethanol and diethyl ether	(Lide and Frederikse, 1996)

5.8	Solubility in fat	Partition coefficient n-octanol/water log P_{ow}: –0.25 (measured)	(Hoechst, 1994)
5.9	pH value	4 (110 g/l at 20 °C)	(Hoechst, 1991)
5.10	Conversion factor	1 ml/m³ (ppm) ≙ 5.31 mg/m³ 1 mg/m³ ≙ 0.19 ml/m³ (ppm) (at 1013 hPa and 25 °C)	

6 Uses

In the manufacture of dyestuffs, pesticides, pharmaceuticals, stabilisers, photographic chemicals; as a component of varnishes and as a solvent; as an additive in fragrances (Riemenschneider, 1987).

7 Experimental results

7.1 Toxicokinetics and metabolism

Valid data on the toxicokinetics and metabolism of acetoacetic acid ethyl ester are scanty. The physical and chemical properties of the substance and the available results from animal studies indicate bioavailability. There are no quantitative data on the absorption, distribution in the body or excretion of acetoacetic acid ethyl ester.

Furthermore, the metabolism of acetoacetic acid ethyl ester is the subject of mere conjecture. Presumably, the ester undergoes cleavage into acetic acid and ethyl alcohol as soon as it enters the body, but the extent and rate of hydrolysis are unknown. Acetoacetic acid is a natural intermediate of fatty acid catabolism and is broken down into CO_2 and water in the body. Possible additional metabolites include β-hydroxybutyric acid and acetone. Ethyl alcohol also undergoes metabolisation to CO_2 and water in the body.

In a study conducted in male rats which were fasted for 24 hours prior to the first dose, oral administration by stomach tube of acetoacetic acid ethyl ester at 4.2, 8.4 and 33.7 g/m² body surface (equivalent to 0.66, 1.31 and 5.26 g/kg body weight, respectively, based on a rat body surface of 312 cm² and body weight of 200 g) in two divided doses daily for 4 to 6 days led to increased urinary excretion of acetone bodies, which were determined as a

measure of absorption and metabolisation of the ester. At the high dose level of 5.26 g/kg body weight, the increase in acetone bodies was about 12% of the administered amount of acetoacetic acid ethyl ester, starting on day 1 of the 4-day administration. A dose of 1.31 g/kg body weight resulted in ketonuria which was equivalent to 14% of the administered acetoacetic acid ethyl ester on day 2 of treatment and further increased to 21% on day 5. The 0.66 g/kg body weight dose showed no effect compared with the control. When an equimolar amount of sodium acetoacetate was used instead of the ester, the increase in ketonuria was twice as high. The investigators concluded from their data that, following oral administration, acetoacetic acid ethyl ester is absorbed by the body and undergoes normal metabolism as the ketonuria in fasting animals was considerably increased. According to their report, no acetoacetic acid was excreted, but 80 to 85% of the isolated acetone bodies were attributed to β-hydroxybutyric acid (Deuel et al., 1936).

3-^{14}C-Acetoacetic acid ethyl ester was administered intraduodenally to male rabbits (approx. 2 kg) which had been made diabetic by injection of a 3.6 ml/kg body weight dose of a 5-percent aqueous alloxan monohydrate solution into the auricular veins and furnished with bile fistulas. Within a period of 24 hours, 2.7% of the administered radioactivity was recovered from the bile as acetone bodies, compared with 1.5% in the controls. Ninety percent of the radioactivity was measured within the first 6 hours after dosing. The peak value occurred just one hour after administration (no further details; Asagoe et al., 1968).

7.2 Acute and subacute toxicity

Upon single oral administration and dermal application, the following LD_{50} values were determined.

Beginning of Table 1

Table 1. Acute toxicity of acetoacetic acid ethyl ester			
Species	Route	LD_{50} (mg/kg b. w.)	Reference
Rat	oral	3980	Smyth et al., 1949
Rat (4 ♂, 4 ♀)	oral	> 3200	Eastman Kodak, 1982
Rat (♂)	oral	12300	Bio-Toxicology, 1975
Rat (♀)	oral	10800	Bio-Toxicology, 1975
Mouse (♂)	oral	3200 to 6400	Eastman Kodak, 1989
Rabbit	dermal	> 10300	Smyth et al., 1949

Table 1. Acute toxicity of acetoacetic acid ethyl ester			
Species	Route	LD_{50} (mg/kg b. w.)	Reference
Rabbit	dermal	> 5000	Moreno, 1973
Rabbit	dermal	> 10000	SIDS, 1990
Guinea pig	dermal	> 20 ml/kg body weight (≙ approx. 20000 mg/kg body weight)	Eastman Kodak, 1982
Rat	inhalation (6 hours)	> 1129 ppm (≙ > 5995 mg/m³)	SIDS, 1990

End of Table 1

In an inhalation risk test, acetoacetic acid ethyl ester was not fatal to rats (n = 6) after 8-hour exposure (no further details; Smyth et al., 1949).

Signs of intoxication were reported only in rare cases. In a study on the acute oral toxicity of acetoacetic acid ethyl ester with groups of 5 male and 5 female rats/dose, doses of 2000 and 4000 mg/kg body weight were observed to cause moderate diarrhoea, whilst at 8000 mg/kg body weight moderate to severe diarrhoea and lethargy were noted. At 10000 mg/kg body weight, 1 out of 5 males and 2 out of 5 females died. All animals exhibited rapid erratic respiration, severe diarrhoea, lethargy and ruffled and unkempt coats. At 16000 mg/kg body weight, all animals succumbed within 30 minutes (Bio-Toxicology, 1975).

Two male mice given oral treatment with acetoacetic acid ethyl ester at 6400 mg/kg body weight were observed to develop severe ataxia, weakness, gasping and convulsions (Eastman Kodak, 1989).

In a 16-day subacute toxicity study, groups of 5 rats received a total of 12 treatments with undiluted acetoacetic acid ethyl ester by gavage at dose levels of 0 (controls), 100 or 1000 mg/kg body weight on 5 days/week. No changes were observed with respect to feed intake, body weight gain, macroscopic and microscopic examination, organ weights and haematology and clinical chemistry parameters (no further details; Eastman Kodak, 1982).

In a subacute toxicity study, groups of 16 male and 16 female Sprague-Dawley rats (about 21 days old at the beginning of the study) were fed a diet containing microencapsulated acetoacetic acid ethyl ester at concentrations of 0 (controls), 100, 300 or 1000 mg/kg body weight on 28 or 29 consecutive days (calculated from the animals' food intake and body weight and from the analysis of the feed for its acetoacetic acid ethyl ester content). Food intake and body weights were unaffected. During the last

week of treatment, the urine of each animal was collected and comprehensively examined. On treatment day 28 or 29, the animals were sacrificed. Blood samples were collected for haematological examination (haemoglobin, blood counts, clotting time) and full serum analysis. At post-mortem, the weights of the brain, heart, caecum, kidneys, adrenal glands, gonads, spleen and liver were recorded. These organs and another 31 tissues were retained in formalin and, in the case of the control and 1000 mg/kg groups, histopathologically examined. The males of the 1000 mg/kg dose group had increased caecum weights, but the histopathological results were normal. All haematology and clinical chemistry parameters and urinalysis findings were in the normal range. Histopathologically, an increased incidence of “nephrocalcinosis” was observed in the female rats of the 1000 mg/kg group, while proteinaceous casts were noted in the urinary bladders of the male rats of that dose group. However, these findings were not considered to be treatment-related. Additional tests (urinary dilution and concentration tests) gave no indications that renal function was impaired. In the overall evaluation, the study findings were considered to be of no toxicological relevance (BIBRA, 1988; Cook et al., 1992).

In a further subacute toxicity study carried out in accordance with OECD guideline No. 407, groups of 5 male and 5 female Sprague-Dawley rats (initial weights 172 to 198 and 142 to 174 g, respectively) were given acetoacetic acid ethyl ester (99.6% pure) by gavage at dose levels of 0 (controls), 50, 225 or 1000 mg/kg body weight every day for 4 weeks. Additional control and top-dose groups of 5 male and 5 female rats were placed under observation for a period of 14 days. Again, even the rats of the high dose group given 1000 mg/kg body weight (the maximum dose level recommended by the OECD) showed no substance-related findings (Hazleton, 1991).

7.3 Skin and mucous membrane effects

Skin irritation studies

In a skin irritation study carried out in accordance with OECD guideline No. 404, 3 albino New Zealand rabbits had 0.5 ml acetoacetic acid ethyl ester applied under semi-occlusive cover to the intact skin of the dorsal to lateral area of the trunk, which had been clipped one day before the beginning of the study. The exposure period was 4 hours. Assessment of the

skin at 0.5, 1, 24, 48 and 72 hours after removal of the patch gave no indications of irritation (irritation index 0 out of a maximum irritation index of 8; Hoechst, 1983 a).

The application of a patch coated with 0.5 ml acetoacetic acid ethyl ester to the clipped dorsal skin of 5 rabbits for 24 hours caused mild hyperaemia (Smyth et al., 1949).

In the rabbit, 510 mg acetoacetic acid ethyl ester caused mild irritation in an open epicutaneous test (no further details; Union Carbide, 1969).

When acetoacetic acid ethyl ester was applied to the intact or abraded rabbit skin under occlusive cover for 24 hours, no irritation was observed (no further details; Moreno, 1973).

Following application of acetoacetic acid ethyl ester to the depilated abdomen of 3 guinea pigs under occlusive cover for 24 hours, there was mild irritation. Daily, open application of acetoacetic acid ethyl ester to the clipped dorsal skin of 5 guinea pigs for a period of 10 days, initially produced minute vesiculation which was only slightly exacerbated by the subsequent treatments (no further details; Eastman Kodak, 1982).

Studies on mucous membrane effects

In order to test the irritating potential to the eye in accordance with OECD guideline No. 405, 3 albino New Zealand rabbits were each given a single instillation of 0.1 ml acetoacetic acid ethyl ester into the conjunctival sac of the left eye. The untreated eye served as the control. The eyes were rinsed 24 hours after instillation. Assessments were carried out 1, 24, 48 and 72 hours following instillation. At 1 and 24 hours after instillation, the conjunctivae were slightly to distinctly swollen and had a slight to diffuse crimson-red colour. In one of the animals, discharge was seen. In addition, 1 out of 3 animals had a reddened iris at 24 and 48 hours after instillation. The irritation had cleared up 72 hours after instillation. Assessment of the cornea in the fluorescein test 24 and 72 hours after instillation revealed no pathological findings (Hoechst, 1983 b). The substance therefore proved to be mildly irritating to the eye.

In another study, instillation of 0.1 ml acetoacetic acid ethyl ester into the conjunctival sac of the eye produced moderate irritation in 2 out of 3 rabbits

and strong irritation in one rabbit. That animal had reddening of the cornea after one hour and corneal opacity after 24 hours. The eye was normal again after 2 weeks (Eastman Kodak, 1982).

In a further study, 100 mg acetoacetic acid ethyl ester was moderately irritating to the rabbit eye within 24 hours (no further details; Marhold, 1986).

According to another study, which was not carried out in accordance with current guidelines for testing, 0.1 ml acetoacetic acid ethyl ester caused severe damage to the rabbit eye (no further details; Carpenter and Smyth, 1946). This finding must be viewed with reservation.

An in-vitro study using isolated bovine cornea gave comparable results. The cornea was obtained by dissection and mounted in a holder which permitted the cornea to be kept in the medium from below while exposing it to the test substance from above. Acetoacetic acid ethyl ester was used in the pure, undiluted form. After 10 minutes' incubation in a horizontal position, the test substance was removed and the surface of the cornea washed with medium. Corneal opacity and permeability to an undiluted fluorescein solution were determined as a measure of ocular damage. Acetoacetic acid ethyl ester exhibited moderate eye irritation in this test. In a parallel in-vivo study, in which the test substance was instilled into the rabbit eye and the animals were placed under observation for up to 21 days, acetoacetic acid ethyl ester was also found to produce moderate eye irritation which was fully reversible after 7 days (Gautheron et al., 1994).

In addition, a modified in-vitro HET-CAM assay was carried out, in which undiluted acetoacetic acid ethyl ester was applied to the chorioallantoic membrane of hen's eggs which had been incubated for 10 days. Haemorrhages, lysis or coagulations in the membrane were determined, the results corresponding to the findings reported by Gautheron et al. (1994; Gilleron et al., 1996).

7.4 Sensitisation

Acetoacetic acid ethyl ester was investigated in the Magnusson and Kligman maximisation test on the guinea pig skin and found not to be sensitising in 10 out of 10 animals (no further details; Eastman Kodak, 1982).

A further study, which was carried out in 1981 to investigate the skin-sensitising potential of acetoacetic acid ethyl ester, employed the “footpad method” in guinea pigs, a method which is no longer in use today. In the primary irritation portion of the study, which was carried out in 5 females that had previously been treated with Freund’s adjuvant, it was noted that application of a 1-percent solution of the test substance in acetone, dioxane and guinea pig fat (7 : 2 : 1) produced signs of inflammation including mild to moderate oedema following observation periods of 24 and 48 hours. The concentration of test substance used for the challenge in the main sensitisation study was set at 0.1% in the above-mentioned vehicle. Ten male guinea pigs were injected in the footpad once with 0.05 ml Freund’s adjuvant without acetoacetic acid ethyl ester (controls) while 10 others were similarly injected with 0.05 ml Freund’s adjuvant containing 1% acetoacetic acid ethyl ester. Seven days later, all animals were treated with 0.3 ml of the 0.1-percent test substance solution. Both the control group and the test group showed slight skin reactions, but there was no difference between the responses. Acetoacetic acid ethyl ester was therefore considered not to be a dermal sensitiser (Eastman Kodak, 1997).

7.5 Subchronic and chronic toxicity

No information available.

7.6 Genotoxicity

7.6.1 In vitro

Acetoacetic acid ethyl ester (100% pure) was tested for mutagenic potential at concentration levels of up to 25000 µg/plate in the Salmonella/microsome assay using *Salmonella typhimurium* strains TA 92, TA 94, TA 98, TA 100, TA 1535 and TA 1537. The tests (preincubation tests) were carried out in the presence and absence of metabolic activation (S9 mix from Kanechlor KC400-induced rat liver). The high concentration levels produced no bacteriotoxicity. Two plates were used per concentration and strain. No mutagenicity was detected (Ishidate et al., 1984).

A further Salmonella/microsome assay was carried out in *Salmonella typhimurium* strains TA 97 and TA 102 to test acetoacetic acid ethyl ester for its

mutagenic potential. This test was also performed in the presence and absence of S9 mix from Aroclor 1254-induced rat liver). Acetoacetic acid ethyl ester was tested at concentration levels of 0, 100, 500, 1000, 5000 and 10000 µg/plate with the result that the revertant counts were not increased relative to the control in any of the cases (Fujita and Sasaki, 1987).

In the context of a publication by the Japanese chemical industry, a further Salmonella/microsome assay (preincubation test) is described which was carried out with acetoacetic acid ethyl ester. The study employed strains TA 98, TA 1535, TA 1537 and TA 1538 and S9 mix from phenobarbital- and 5,6-benzoflavone-induced rat livers. Acetoacetic acid ethyl ester concentrations of 20 to 5000 µg/plate did not produce any mutagenic effects (JETOC, 1996).

A further Salmonella/microsome assay was carried out as a standard-plate incorporation test in *Salmonella typhimurium* strains TA 100, TA 1535, TA 1537 and TA 98 both with and without metabolic activation (S9 mix from Aroclor 1254-induced rat liver). The purity of the acetoacetic acid ethyl ester used was greater than 99% (by weight), and the 6 concentrations tested ranged between 4 and 5000 µg/plate. There was no bacteriotoxicity even at 5000 µg/plate. Acetoacetic acid ethyl ester proved not to be mutagenic in this study (Hoechst, 1988).

Acetoacetic acid ethyl ester showed genotoxicity in the direct plate test on *Escherichia coli* WP2uvrA (trp–) at concentration levels of 200 µg/plate and above. In this study, test concentrations were in the range from 25 to 1600 µg/plate. The mutagenic effect exhibited linear concentration-dependency. Three parallel investigations were carried out (no further details; Yoo, 1986).

In contrast, acetoacetic acid ethyl ester (> 99% pure) proved negative in another test on *Escherichia coli* WP2uvrA which was performed with and without metabolic activation (S9 mix from Aroclor 1254-induced rat liver). The test concentrations ranged from 4 to 5000 µg/plate. There was no bacteriotoxicity even at 5000 µg/plate (Hoechst, 1988).

In a DNA repair test in *Bacillus subtilis* strains M (rec–) and M (rec+), exposure to acetoacetic acid ethyl ester was not observed to produce any effect at 20 µg/plate (no further details; Oda et al., 1978).

A further DNA repair study on *Bacillus subtilis* strains M45 (rec–) and M27 (rec+) gave a positive result. The concentration of acetoacetic acid ethyl ester used in this case was 20 µl/plate (equivalent to 20.6 µg/plate). Again, the publication provides no experimental details of the testing procedures (Yoo, 1986).

In an in-vitro study conducted to assess chromosomal damage to Chinese hamster lung fibroblasts (CHL cell line), acetoacetic acid ethyl ester (100% pure) did not lead to an increased aberration or polyploidy rate. The 2000 µg/ml test concentration was the highest dose not to cause cytotoxicity. The cells were examined 24 and 48 hours after the beginning of treatment. The test was carried out in the absence of metabolic activation, and only 100 metaphases/concentration level were evaluated, thus limiting the validity of the results (Ishidate et al., 1984).

In *Saccharomyces cerevisiae* D61.M, acetoacetic acid ethyl ester (99%) did not increase mitotic recombination when tested in two independent studies. The concentrations tested, 2550 to 20000 µg/ml, covered the range from weak inhibition of growth to 100% cytotoxicity. The assay was carried out without metabolic activation (Zimmermann et al., 1989).

7.6.2 In vivo

No information available.

7.7 Carcinogenicity

No information available.

7.8 Reproductive toxicity

No information available.

7.9 Effects on the immune system

No information available.

7.10 Neurotoxicity

No information available.

7.11 Other effects

Groups of 3 Wistar rats (28 to 39 g), about 2 weeks old, inhaled 7.8 x 10^{-8} M acetoacetic acid ethyl ester (equivalent to approx. 10 µg, not specified whether per litre or m^3, but presumably per litre) for periods of 4 or 8 weeks (duration of daily exposure not specified). Subsequently, the olfactory bulb was examined by light and electron microscopy. A specific pattern of degeneration was noted in the mitral cells of the olfactory bulb. After a comparative study of a total of 44 “odours”, this finding proved not to be concentration-dependent and was observed to be comparable to that obtained with heptanol, cyclohexanol, cyclohexanone, menthol or naphthaline (Pinching and Døving, 1974). The significance of these findings is unclear.

Five male Wistar rats were continually exposed to acetoacetic acid ethyl ester-containing atmosphere (whole-body exposure, concentration not specified) from the day they were born for a period of 32 or 33 days. The diameter and layer volume of the olfactory glomeruli were reduced and they exhibited a statistically significant increase in density (no further details; Royet et al., 1989).

In the open-chest anaesthetised cat maintained under positive-pressure ventilation, intravenous and intra-arterial administration of acetoacetic acid ethyl ester doses of 100 to 200 mg/cat (equivalent to about 33 to 67 mg/kg body weight) were followed by dyspnoea and a fall in blood pressure (Barer and Nüsser, 1958).

In an in-vitro study with a Franz diffusion cell, when acetoacetic acid ethyl ester was tested as a vehicle to enhance indomethacin permeation through rat skin, it was found to produce only slight, 5-fold enhancement compared with water whereas acetic acid ethyl ester provided a 1500-fold enhancement (Catz and Friend, 1989).

8 Experience in humans

Dermal application of acetoacetic acid ethyl ester at a concentration of 8% in petrolatum gave no indications of sensitisation in 26 human subjects either in the 48-hour patch test (occlusive) or in the Kligman maximisation test (no further details; Epstein, 1973).

9 Classifications and threshold limit values

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (“MAK-Kommission”) of the Deutsche Forschungsgemeinschaft will investigate the possibility of establishing a MAK value for the chemical (DFG, 2000).

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