The MAK Collection for Occupational Health and Safety

Acrylic acid ethyl ester

MAK Value Documentation, addendum – Translation of the German version from 2016

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Ethyl acrylate / Ethyl prop-2-enoate

MAK Value Documentation

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the maximum concentration at the workplace (MAK value) of ethyl acrylate [140-88-5] of 5 ml/m³, considering all toxicity endpoints. Available unpublished study reports and publications are described in detail. The critical effect of ethyl acrylate is irritation of eye and nose in humans and the olfactory mucosa in rats and mice. The chronic NOAEC in rats is 5 ml/m³. Since 2014 the Commission uses an empirical approach to set MAK values for substances with critical effects on the upper respiratory tract or the eyes. Accordingly, the MAK value has to be lowered to 2 ml/m³, which is confirmed in a recent volunteer study with a NOAEC of 2.5 and a LOAEC of 5 ml ethyl acrylate/m³. As local effects are critical, the assignment to Peak Limitation Category I and the excursion factor of 2 are confirmed. Developmental toxicity studies with ethyl acrylate show no risk for the embryo or foetus if the MAK value is observed, and the assignment to Pregnancy Risk Group C is retained. Ethyl acrylate is not genotoxic in vivo and not carcinogenic. Skin contact may contribute significantly to systemic toxicity and ethyl acrylate is designated with an "H" notation. The available data confirm that the substance is a skin sensitizer and the designation with "Sh" is retained. There are no data concerning the potential for respiratory sensitization.

Keywords

acrylic acid ethyl ester; ethyl acrylate; ethyl propenate; ethyl 2-propenoate; 2-propenoic acid ethyl ester; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; irritation; allergenic effects; reproductive toxicity; fertility; genotoxicity; carcinogenicity; peak limitation; prenatal toxicity; germ cell mutagenicity; absorption through the skin; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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Acrylic acid ethyl ester

[140-88-5]

Supplement 2016

MAK value (2015)	**2 ml/m³ (ppm) ≙ 8.31 mg/m³**
Peak limitation (2000)	**Category I, excursion factor 2**
Absorption through the skin (2015)	**H**
Sensitization (1986)	**Sh**
Carcinogenicity	**–**
Prenatal toxicity (2006)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**
1 ml/m³ ≙ 4.15 mg/m³	**1 mg/m³ ≙ 0.241 ml/m³**

In 1986, the previous MAK value for acrylic acid ethyl ester of 5 ml/m³ was derived on the basis of histopathologically confirmed local irritation of the nose of rats at 25 ml/m³ in a 27-month inhalation study, and from a NOAEC of 5 ml/m³ in a 2-year inhalation study. A NOAEC for sensory irritation in humans was not available. In view of the specific respiratory physiology of rodents, which can only breathe through their noses, and the resultant high local sensitivity, the MAK value of 5 ml/m³ was considered sufficient to protect humans against damage to the airways from irritation. In the meantime, a study with subjects has been carried out, making a re-assessment of the MAK value necessary. In this supplement, the absorption through the skin and the germ cell mutagenicity of acrylic acid ethyl ester are also re-assessed, and the data for sensitization updated.

For acrylic acid ethyl ester, documentation from 1986 is available (documentation "Ethyl acrylate" 1993) as well as supplements from 1999 covering sensitization (supplement "Ethyl acrylate" 2001), another from 2000 on peak limitation (supplement "Ethylacrylat" 2000, available in German only) and the last, dated 2007, on developmental toxicity (supplement "Ethylacrylat" 2007, available in German only).

Toxicokinetics and Metabolism

Dermal application

In an in vitro study of the dermal penetration (Franz' diffusion cell) of acrylic acid ethyl ester, an 1.8 cm^2 area of skin from hairless rats was exposed to 35 µl undiluted [2,3-^{14}C] acrylic acid ethyl ester (corresponding to 32.2 mg). The donor chamber was sealed with a lid containing a layer of activated carbon to absorb the evaporated acrylic acid ethyl ester. In the analysis carried out 15 minutes after the beginning of the study, 88% of the applied dose was recovered in the layer of activated carbon, on the wall of the donor cell and as vapour above the skin. After 6 hours, the acrylic acid ethyl ester was distributed as follows: 66% in the activated carbon phase or on the wall of the donor cell, 6% in the skin and 21% in the receptor solution. No details are given for the course of penetration over time. Without occlusion, 95% of the acrylic acid ethyl ester evaporated (Tomlinson et al. 1989).

Studies of the quantitative dermal absorption of acrylic acid methyl ester, which is similar in structure and which could be used to estimate the penetration through the skin of acrylic acid ethyl ester, are not described (ECHA 2015).

On the basis of an acrylic acid ethyl ester concentration of 3%, which in the maximization test is considered to be a challenge concentration and therefore as not irritating to the skin (see supplement "Ethyl acrylate" 2001), dermal fluxes of 1.304, 0.116 and 0.146 mg/cm^2 and hour are obtained using the models of Fiserova-Bergerova et al. (1990), Guy and Potts (1993) and Wilschut et al. (1995), respectively. After the exposure of both hands and forearms for one hour (about 2000 cm^2), this would correspond to the total uptake of 2608, 232 and 290 mg acrylic acid ethyl ester, respectively.

Effects in Humans

Single exposures

In a study with subjects, five exposures lasting 4 hours each with different ambient air concentrations were investigated. The 9 men and 10 women (average age 25.2 and 22.4 years, respectively) were exposed either to a constant concentration of 0, 2.5 or 5 ml acrylic acid ethyl ester/m^3 or alternating concentration sequences of 0 to 5 ml/m^3 (mean concentration C_{TWA} 2.5 ml/m^3; TWA: time weighted average) and 0 to 10 ml/m^3 (C_{TWA} 5 ml/m^3). Effects on the health resulting from chemosensory irritation caused by acrylic acid ethyl ester were investigated and recorded using physiological parameters, data from subjective experience and behavioural tests. In the area of experienced effects, the level of experience was scaled (olfactory experiences: odour intensity, annoyance, disgust; trigeminal experiences: pungency, burning, sharpness to the eyes and nose) and a standardized record of health symptoms (for example, headaches, reddening of the eyes) was used. The investigated physiological parameters included the frequency of blinking, changes in the nasal airway resistance/narrowing of the main nasal cavity and neurogenic inflammatory parameters (substance P) in the nasal lavage. The selected test procedures for investigating be-

havioral effects comprised tasks examining working memory, divided attention and the flanking stimulus.

Subjectively, under all four of the exposure conditions to acrylic acid ethyl ester, the odour intensity and annoyance level were experienced as being strong. Especially during the two variable exposures, the assessments of olfactory experiences (odour intensity and annoyance) were markedly increased. With increasing exposure duration, at both the constant and the variable concentration condition of C_{TWA} 5 ml/m³, an increase in trigeminally mediated effects (for example, eye irritation) was observed; especially with exposure peaks of 10 ml/m³, the participants reported pronounced irritation of the eyes. Rhinomanometry (examination of the narrowing of the main nasal cavity) did not reveal a systematic effect pattern. As regards the blinking frequency, changes were found which fitted the exposure patterns and the subjective estimates. Under the variable 5 ml/m³ exposure condition, the blinking frequency was significantly increased compared with the control condition (23.2 min^{-1} compared with 17.7 min^{-1}). The exposure peak at the end of this condition (10 ml/m³) produced an increase in the mean blinking frequency to almost 30 min^{-1}. Analysis of the nasal lavage fluid revealed a trend towards initial signs of neurogenic inflammation, measured as the increase in substance P, in both exposures with a C_{TWA} of 5 ml/m³. With a constant or variable C_{TWA} of 2.5 ml/m³, these effects were not found. Changes in performance were not seen in the behavioural tests. However, in all task parameters, there was also a tendency towards a reduction in performance at the highest exposure level. In the most difficult version of the working memory test, the subjects made significantly more mistakes under the 5 ml/m³ C_{TWA} conditions than under control conditions (Blaszkewicz et al. 2010). From this study, a LOAEC for irritation of the eyes and nose was obtained of 5 ml/m³ after constant or variable exposure with twice as high concentration peaks, and a NOAEC of 2.5 ml/m³ under the same exposure conditions.

Repeated exposure

In another study available to the Commission in the form of unpublished interim reports, the possible cumulation of chemosensory effects from alternating concentration sequences (0–10 ml acrylic acid ethyl ester/m³, C_{TWA} 5 ml/m³) was investigated during repeated exposures on 5 consecutive days (one working week). In these experiments with a total of 16 women and 14 men aged between 18 and 35 years, the critical effects, an increase in blinking frequency, could be replicated and the increase in the substance P concentration in the nasal lavage fluid could be statistically confirmed. While the concentration of the neuropeptide increased only by an average of 3% on the days on which the study was carried out with exposure to ambient air (0 ml/m³), the average increase on the study days with exposures to 5 ml acrylic acid ethyl ester/m³ was 38%. A cumulation of the effects could not be observed during the repeated exposure for either this physiological marker of incipient neurogenic inflammation, or the concentration-dependent increase in blinking frequency (Blaszkewicz et al. 2012, 2013).

In a prospective cohort study, 60 workers employed in the production of acrylic acid, acrylic acid esters and acrylate dispersions, and 60 workers not exposed as control persons were examined in the period between 1992 and 1999. The average

exposure duration was 13 ± 5 years. Exposure to acrylonitrile, *n*-butyl alcohol, butyl acrylate, acrylic acid ethyl ester, acrylic acid methyl ester, methacrylic acid methyl ester, toluene and styrene were recorded using passive personal dosimetry. The measured concentrations of all substances were generally low. Eighty % of the personal air sample results for acrylic acid ethyl ester were below 0.05 ml/m^3, 10% were between 0.05 and 0.24 ml/m^3. The maximum concentrations were 2.4 ml/m^3. The results of clinical, haematological and biochemical examinations revealed no differences between the group of exposed workers and the group of control persons, which could be attributed to exposure to the chemicals mentioned above. Cytogenetic examination of the peripheral lymphocytes of the exposed workers did not reveal genotoxic effects in pairwise comparisons. Throughout the entire period, the number of chromosomal aberrations in the exposed workers was higher than that in the controls; the increase was statistically significant (Tuček et al. 2002; Williams and Iatropoulos 2009). As no differentiation was made regarding smoking habits, and exposure was to a mixture of substances, the results of this study cannot be seen as evidence of a genotoxic effect of acrylic acid ethyl ester.

Local effects on skin and mucous membranes

Acrylic acid ethyl ester is irritating to the skin and mucous membranes of the eyes and airways (documentation "Ethyl acrylate" 1993).

Allergenic effects

The sensitizing effects of acrylic acid ethyl ester on the skin in humans has been demonstrated in several reports by positive patch test results and in some cases by the sensitization induced as a result of patch testing (supplement "Ethyl acrylate" 2001). Since the supplement from 1999, numerous case reports with positive patch test results have been published (for example Brandao 2001; Torres et al. 2005; Vogel et al. 2014) and a few other clinico-epidemiological investigations in smaller collectives (for example Christoffers et al. 2013; Drucker and Pratt 2011; Ramos et al. 2014; Sood and Taylor 2003).

Data for respiratory sensitization are still not available.

Carcinogenicity

In two American plants producing acrylic glass, mortality studies were carried out in three cohorts of workers who had worked in the factories between 1933 and 1982 (Walker et al. 1991). The main exposure was to acrylic acid ethyl ester and methacrylic acid methyl ester; when recording the exposure, no differentiation was made between the substances. Exposure measurements were initiated in 1972 in one of the two sites, the previous data were reconstructed from production records and by questioning the employees. Among other substances, the workers were also exposed to 1,2-dichloroethane, dichloromethane and acrylonitrile. An increased incidence of colon cancer was most apparent in the workers of the earliest production

period and in workers with the highest exposure. An increase in the incidence of rectal cancer was found in the first plant; this was, however, not significant. An increase in mortality from colon cancer was found to be significant in one plant, but in the other plant was not significant. There was, however, no relationship between the tumour risk and increasing exposure to acrylic acid ethyl ester. Because the exposure levels were not determined, no differentiation between exposure to acrylic acid ethyl ester and to methacrylic acid methyl ester was made, co-exposure to other substances considered as possibly carcinogenic to humans occurred, and other shortcomings were evident (DECOS 2012), this study cannot be included in the evaluation of the carcinogenicity of acrylic acid ethyl ester.

In a review in which the epidemiological data for possible carcinogenic effects of methacrylic acid methyl ester in humans are summarized, no additional data are given which would indicate that acrylic acid ethyl ester is a human carcinogen. Furthermore, in this publication the results from the cohort study (see above) are regarded as unexplained (Tomensson et al. 2005).

Animal Experiments and in vitro Studies

Acute toxicity

Inhalation

The RD_{50} of acrylic acid ethyl ester in mice is 315 ml/m^3 (documentation "Ethyl acrylate" 1993).

Dermal application

The minimum lethal dose after dermal application of acrylic acid ethyl ester was higher than 600 µmol/animal (2000 mg/kg body weight) in the transgenic mouse strain Tg.AC(v-Ha-ras) (Nylander-French and French 1998).

Subacute, subchronic and chronic toxicity

Oral administration

Oral treatment of F344 rats and B6C3F1 mice with acrylic acid ethyl ester doses of 0, 100 or 200 mg/kg body weight for 2 years produced an increased incidence of squamous cell carcinomas or papillomas in the forestomach. In addition, substance-related, non-neoplastic changes were found such as epithelial hyperplasia and hyperkeratosis, but no signs of systemic toxicity (documentation "Ethyl acrylate" 1993).

Further studies with rats showed that the increased incidence of forestomach neoplasms correlates with the incidence of marked and continuous hyperplasia and cell proliferation of the mucous membrane, which can possibly be attributed to the pronounced depletion of important cellular thiols, particularly of glutathione (SCOEL 2004).

Allergenic effects

Sensitizing effects on the skin

In female CBA/Ca mice, a local lymph node assay with 10%, 25% or 50% acrylic acid ethyl ester in acetone/olive oil (4:1) produced stimulation indices of about 1.2, 2.7 and 5.0, respectively. The concentration estimated to induce a three-fold increase in lymphocyte proliferation (EC_3 value) was 28.7% (Warbrick et al. 2001).

In another local lymph node assay with CBA/Ca mice, an EC_3 value of 36.8% was calculated for acrylic acid ethyl ester in the same vehicle (Dearman et al. 2007).

In an earlier study, acrylic acid ethyl ester concentrations of up to 30% did not increase lymphocyte proliferation in female B6C3F1 mice compared with that observed in controls (Hayes and Meade 1999).

Negative results were obtained with the same concentration also in a mouse ear swelling test (Hayes and Meade 1999).

Sensitizing effects on the airways

There are no data available.

Reproductive and developmental toxicity

Developmental toxicity

There are no new studies available for the developmental toxicity of the substance. In two inhalation studies with female Sprague Dawley rats already described in the supplement of 2007, the NOAECs for developmental toxicity and maternal toxicity were 50 and 100 ml/m^3. In the earlier study there was a slight, but not statistically significant increase in malformations after concentrations of 150 ml/m^3. In the second valid study, reduced foetal weights with reduced maternal body weight gains were found at 200 ml/m^3. There were, however, no malformations.

Genotoxicity

The data available for acrylic acid ethyl ester are presented in summarized form. The results already described in the documentation of 1986 (documentation "Ethyl acrylate" 1993) are also included.

In vitro

In vitro, in a cell-free system, acrylic acid ethyl ester does not bind to deoxyribonucleic acid (IARC 1999).

Acrylic acid ethyl ester did not induce mutations in bacteria, but induced mitotic recombination in Saccharomyces cerevisiae (IARC 1999). In CHL cells, SCE were induced in the presence, but not in the absence, of a metabolic activation system (NTP 1998). When splenocytes of mice were treated either during the G0 phase of the cell cycle or 23 hours after mitogenic stimulation during the late G1 or the early

S phase, the results of the SCE test were negative. A significant increase in aberrations of the chromatid type was found in the cells that were treated 23 hours after mitogenic stimulation (NTP 1998). The induction of chromosomal aberrations was found in L5178Y mouse lymphoma cells, CHO cells and CHL cells. In the $TK^{+/-}$ test with L5178Y mouse lymphoma cells, small colonies were induced, which indicates clastogenic effects or cytotoxicity. In another investigation a concentration-dependent increase in the frequency of mutations at the tk locus was observed. Single strand breaks were not found, although apoptosis and double strand breaks indicated necrosis at high concentrations. DNA double strand breaks with high and with low molecular weight could be detected, but also only at the highest concentrations. It could thus be demonstrated that the mutagenicity of acrylic acid ethyl ester correlates with its cytotoxicity, which is based on GSH depletion and a disturbance in the mitochondrial membrane function (Ciaccio et al. 1998; DECOS 2012). In the HPRT test with CHO cells, no mutations were induced. In mammalian cells, tests were performed mainly in the absence of a metabolic activation system (SCOEL 2004).

In vivo

In Drosophila melanogaster, the results of the SLRL test with dietary administration (40 000 mg/kg feed) or injection of 20 mg/ml were negative (NTP 1998).

In the forestomach or in the liver of male F344 rats given gavage doses of acrylic acid ethyl ester of 400 mg/kg body weight, no DNA strand breaks could be found (SCOEL 2004). After repeated dermal application of 0, 60, 300 or 600 µM acrylic acid ethyl ester (0, 200, 1000 or 2000 mg/kg body weight, 3 times a week, for 20 weeks) no induction of DNA strand breaks could be detected in the peripheral blood of female Tg.AC mice using the comet assay. The authors of the publication interpreted their results as indicating that acrylic acid ethyl ester is either not genotoxic or that the amount that penetrates the skin is not sufficient to cause demonstrable systemic effects (Tice et al. 1997). Model calculations, however, have shown that dermal penetration can indeed play a role in the systemic effects (see Manifesto (MAK value/classification)).

In mouse splenocytes, neither SCE nor chromosomal aberrations were induced after single intraperitoneal injections of up to 1000 mg acrylic acid ethyl ester/kg body weight. However, at the highest dose level, a slight, statistically significant increase in the incidence of micronuclei was found, which is probably attributable to a pronounced increase in one animal. In a micronucleus test with 4 male Balb/c mice per group, a dose-dependent increase in polychromatic erythrocytes containing micronuclei was found after intraperitoneal injection of a total dose of 225 to 1800 mg/kg body weight, administered 24 hours apart. Two of the four animals in the high dose group died, and in all the groups, with the exception of the low dose group, the ratio between polychromatic and normochromatic erythrocytes was reduced, indicating toxic effects in the bone marrow. These positive test results could not be reproduced in a further study with intraperitoneal injection in Balb/c and C57BL/6 mice (10/group; 2 × 738 mg/kg body weight or 2 × 812 mg/kg body weight). In another micronucleus test with intraperitoneal injection in male BDF1 mice, there were likewise no increased incidences of micronuclei in the bone mar-

row of the treated animals up to 1000 mg/kg body weight. After gavage administration, the test yielded negative results up to the highest dose tested of 1000 mg/kg body weight, and dermal application did not lead to the induction of micronuclei in female Tg.AC mice (see above) (SCOEL 2004; Tice et al. 1997).

Carcinogenicity

Acrylic acid ethyl ester induced cell transformations in cultured tracheal cells of rats (NTP 1998).

Acrylic acid ethyl ester was not found to have carcinogenic potential following inhalation exposure, dermal application or administration with the drinking water. The increased incidence of forestomach tumours in rats and mice found after gavage administration can clearly be attributed to the chronic irritation caused by the acrylic acid ethyl ester dissolved in oil (documentation "Ethyl acrylate" 1993).

In 1998, acrylic acid ethyl ester was included by the NTP (National Toxicology Program) for the last time in the list of substances considered to be proven or probable human carcinogens. It was deleted from this list in 2005 (NTP 2014; Williams and Iatropoulos 2009).

In two studies, acrylic acid ethyl ester was tested in transgenic Tg.AC(v-Ha-ras) mice, a strain which responds? to dermal treatment with either non-genotoxic or genotoxic carcinogens with the rapid formation of papillomas. In one study, doses of 0, 60, 300 or 600 µmol acrylic acid ethyl ester/animal (0, 200, 1000 or 2000 mg/kg body weight) were applied to the shaved dorsal skin of 10 female mice, 3 times a week, for 20 weeks. There are no details of the dosage available for the second study. In both cases, treatment with acrylic acid ethyl ester did not induce the formation of papillomas. The tests with tripropylene glycol diacrylate, on the other hand, yielded positive results (DECOS 2012; Nylander-French and French 1998).

Manifesto (MAK value/classification)

The critical effect of acrylic acid ethyl ester is local irritation of the eyes and nose in humans and of the olfactory epithelium in rats and mice.

MAK value. In 1986, the previous MAK value of 5 ml/m^3 was derived from the 27-month inhalation study as a result of histopathologically confirmed local irritation of the nose of rats at 25 ml/m^3, and a NOAEC of 5 ml/m^3 from the 2-year inhalation study. A NOAEC for sensory irritation in humans was not available at the time. In view of the special respiratory physiology of rodents, which can only breath through their noses, and the resulting high local sensitivity, the MAK value of 5 ml/m^3 was considered to be sufficient to protect humans against damage to the airways from irritation (documentation "Ethyl acrylate" 1993).

In a study with subjects carried out in 2010 under several different 4-hour exposure conditions, a LOAEC of 5 ml/m^3 was obtained with both constant and variable exposure with twice as high concentration peaks, and a NOAEC of 2.5 ml/m^3 for irritation of the eyes and nose under the same exposure conditions. The LOAEC of 5 ml/m^3 from variable exposure could be reproduced in a further study with sub-

jects. These results show that the previous MAK value of 5 ml/m³ was too high. The NOAEC in these studies was 2.5 ml/m³. As no cumulation of effects over time was found, the MAK value based on the NOAEC has been lowered to 2 ml/m³ according to the preferred value approach. The odour intensity and annoyance, which were regarded as strong by the subjects even at an average concentration of 2.5 ml/m³, although there is a tendency towards adaptation during the exposure, are not taken into account in the evaluation of the MAK value.

Peak limitation. Classification of the substance in Peak Limitation Category I has been retained because of its local effects. As no irritation of the eyes and nose could be found in subjects after 4-hour exposure to an average concentration of 2.5 ml/m³ with twice as high peak concentrations, an excursion factor of 2 has been established.

Prenatal toxicity. No new studies of the developmental toxicity of the substance are available, so that two studies with female Sprague Dawley rats already described in the supplement of 2007 have been used to assess its prenatal toxicity. In the earlier study, there was a slight, but not statistically significant increase in malformations at 150 ml/m³. In the second study, at 200 ml/m³, reduced foetal weights were found with reduced maternal body weight gains, but no malformations. The NOAECs for developmental toxicity and maternal toxicity were 50 ml/m³ and 100 ml/m³, respectively. The 25-fold and 50-fold differences between these NOAECs and the MAK value of 2 ml/m³ are sufficiently large, so that no embryotoxic effects are to be expected when the MAK value is observed. The classification of acrylic acid ethyl ester in Pregnancy Risk Group C has therefore been retained.

Carcinogenicity. There are no reliable data available for the carcinogenicity of acrylic acid ethyl ester in humans. In animal studies, acrylic acid ethyl ester was not found to have carcinogenic potential after inhalation exposure, dermal application and administration with the drinking water. The increased incidence of forestomach tumours in rats and mice after gavage administration can clearly be attributed to the chronic irritation caused by acrylic acid ethyl ester dissolved in oil. As before, the substance is therefore not classified in one of the categories for carcinogens.

Germ cell mutagenicity. In bacteria and in mammalian cells, acrylic acid ethyl ester did not induce gene mutations or point mutations. In vitro, acrylic acid ethyl ester had clastogenic effects. The positive results of the in vitro studies of clastogenic effects have not been confirmed in vivo. There are no data available for effects of the substance on germ cells. From the known studies with somatic cells, there is no evidence of germ cell mutagenicity. Acrylic acid ethyl ester is therefore not classified in one of the categories for germ cell mutagens.

Absorption through the skin. Only one, inadequately described, in vitro study is available for the dermal uptake of undiluted acrylic acid ethyl ester. In rabbits, undiluted acrylic acid ethyl ester is irritating to the skin. From model calculations, dermal uptake in the range of 232 to 2608 mg after the exposure of both hands and forearms for one hour to a 3% acrylic acid ethyl ester solution has been estimated. The data from the 2-year study with oral administration of acrylic acid ethyl ester in rats (documentation "Ethyl acrylate" 1993) suggest a systemic, long-term NOAEL

of 200 mg/kg body weight. On the basis of this value and taking into consideration the correction values for the toxikokinetic extrapolation from rats to humans (1:4), a dose of 50 mg/kg body weight is obtained. As this value is derived from an animal experiment (1:2), a tolerable dose for systemic effects in humans of 25 mg/kg body weight is obtained, which for a body weight of 70 kg corresponds to a total exposure to 1750 mg acrylic acid ethyl ester. The results of model calculations show that as a result of dermal absorption this tolerable dose cannot be adhered to safely. Therefore, acrylic acid ethyl ester is designated with an "H".

Sensitization. Several cases of contact sensitization caused by acrylic acid ethyl ester have been reported since the supplement of 1999. Positive results from two local lymph node assays indicate that in this model the substance has only a low allergenic potency. There are still no data available for its sensitizing effects on the airways. Acrylic acid ethyl ester is therefore still designated with "Sh", but not with "Sa".

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