# Oleic acid / (Z)-octadec-9-enoic acid

## MAK Value Documentation

A. Hartwig[1,*], MAK Commission[2,*]

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### Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated oleic acid [112-80-1], which was classified as possible carcinogenic to humans in Carcinogen Category 3A, to derive a maximum concentration at the workplace (MAK value), considering genotoxicity and carcinogenicity. Oleic acid is irritating to the skin if applied repeatedly. It is not mutagenic in vitro, data in vivo are not available. Oleic acid showed skin tumour promoting activity in mice after initiation with 9,10-dimethylbenzanthracen but not without initiation. In a general evaluation of the skin tumour initiation-promotion-test in mice published in 2015, the Commission concluded, that substances which only induce skin tumours after initiation, but not without initiation, do not have to be classified in a Carcinogen Category. Therefore, the former classification of oleic acid is withdrawn. Since it is not possible to derive a MAK value with the available data, oleic acid is assigned to Section II b of the List of MAK and BAT values.

### Keywords

oleic acid; (Z)-9-octadecenoic acid; toxicokinetics; metabolism; irritation; allergenic effects; carcinogenicity; peak limitation; prenatal toxicity; germ cell mutagenicity; absorption through the skin; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

### Author Information

[1] Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Department of Food Chemistry and Toxicology, Institute for Applied Biosciences, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Geb. 50.41, 76131 Karlsruhe, Germany

[2] Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany

* Email: A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)

# Oleic acid

**[112-80-1]**

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|---|---|
| **MAK value** | **not yet established, see Section IIb of the List of MAK and BAT Values** |
| **Peak limitation** | **–** |
| **Absorption through the skin** | **–** |
| **Sensitization** | **–** |
| **Carcinogenicity** | **–** |
| **Prenatal toxicity** | **–** |
| **Germ cell mutagenicity** | **–** |
| **BAT value** | **–** |

Documentation from 2001 is available for oleic acid, in which the substance is classified in Carcinogen category 3A, without any further designations or classifications (documentation "Oleic acid" 2002).

This supplement has been drawn up because the Commission's evaluation of the mouse skin initiation–promotion model and their relevance for dermal carcinogenicity in humans of Schwarz et al. (2015).

## Toxic Effects and Mode of Action

After oral administration, oleic acid is almost completely absorbed, distributed throughout the body and degraded by ß-oxidation to $CO_2$ in fatty acid metabolism. After single applications, oleic acid is not irritating to the skin and mucous membranes. After repeated application of solutions of at least 50% it is slightly irritating to the skin. There are no studies available with longer term oral administration or inhalation of oleic acid alone, from which a no observed adverse effect level (NOAEL) or a no observed adverse effect concentration (NOAEC) can be derived. Oleic acid acts as a tumour promoter on mouse skin; a genotoxic mechanism can be excluded (documentation "Oleic acid" 2002).

There are no new data available for any of the toxicological end points relevant to the evaluation.

## Toxicokinetics and Metabolism

There are no quantitative studies available for dermal absorption of the substance. As there are no data for water solubility and log $K_{OW}$[1)], calculations using mathematical models are not possible, either.

Oleic acid is a penetration enhancer (Trommer and Neubert 2006) which probably acts via fluidization of the lipids in the stratum corneum and phase separation (Naik et al. 1995).

## Local Effects on Skin and Mucous Membranes

After single applications, oleic acid is not irritating to the skin and mucous membranes of rats. It is slightly irritating to the skin of rats after the repeated application of solutions of at least 50%, and irritating in humans after occlusive application for 5 days (documentation "Oleic acid" 2002).

## Allergenic Effects

### Humans

From April 2000 to July 2002, in 5 clinics of the IVDK (Information Network of Departments of Dermatology), 233 patients exposed to metal-working fluids were subjected to patch tests with numerous potential components of metal-working fluids. None of the 229 persons tested produced a reaction to 5% oleic acid in petrolatum; a questionable reaction occurred in one person (Geier et al. 2003).

### Animals

In a local lymph node assay with several unsaturated fatty acids such as linoleic acid, linolenic acid and undecylenic acid, as well as with oleic acid (purity: 99%), stimulation of the lymphocytes was obtained, although without any clear concentration dependency in the case of oleic acid. At concentrations of 10%, 25% and 50% (4:1 in acetone/olive oil), oleic acid produced stimulation indices of 2.6, 14.9 and 6.9, respectively. The authors discussed this formally positive result and suspect that oleic acid does not act as a hapten. As an alternative cause, they suggested oleic acid-induced (observed in vitro) stimulation of non-specific second messenger mechanisms and the resulting induction of pro-inflammatory cytokines (for example, interleukin-1α) (Kreiling et al. 2008).

1) octanol/water partition coefficient

A maximization test (5% oleic acid for intradermal induction, 50% oleic acid for topical induction and 25% oleic acid for the challenge tests) yielded a questionable or borderline positive result, which does not make designation of the substance obligatory. The first challenge test resulted in a reaction in 1 and 4 of 10 animals after 48 and 72 hours, respectively, which was reproducible in only 2 animals. A second challenge test led to reactions in 3 of 10 animals after both 48 and 72 hours. Only 2 animals produced a reaction in both challenge tests (Kreiling et al. 2008).

## Carcinogenicity

In long-term feeding studies in rats, oleic acid increased the incidence of forestomach and intestinal hyperplasia and led to increased incidences of tumours of the pancreas which, however, were not statistically significant. The hyperplasia was regarded as evidence of a local effect in the forestomach and intestine. The incidences of pancreas tumours were in the range of the historical controls. In the initiation–promotion test in mice, oleic acid alone or as a 20% solution in chloroform had a tumour-promoting effect on the skin after initiation with 9,10-dimethylbenzanthracene in liquid paraffin. Without initiation treatment, no tumours occurred (Holsti 1959). As a result of the rapid evaporation of chloroform, the 20% solution was likewise present on the skin in the form of undiluted oleic acid. The tumours were all papillomas, no histologically malignant tumours occurred.

There are no new valid studies available for the carcinogenicity of the substance in general or on the skin in particular.

## Other Effects

Groups of 4 to 6 male and female BDV1 rats were given gavage doses of oleic acid of 0.5 mg/kg body weight and day for 30 days. Then, using a combination of immunoaffinity clean-up and $^{32}P$ postlabelling, it was investigated whether εdA or εdC DNA–etheno adducts had formed in epithelial cells of the colon, in the liver, the prostate, in mammary epithelial cells or in white blood cells. Oleic acid produced a 3 to 9-fold increase in the two etheno adducts only in the prostate (Fang et al. 2007).

## Manifesto (MAK value/classification)

The critical effect is irritation caused by oleic acid after repeated exposure.

**Carcinogenicity.** There are no new data available. In the studies of the carcinogenicity of the substance already described in the documentation from 2001 (documentation "Oleic acid" 2002), oleic acid was found to have a tumour-promoting effect on the skin of mice only after initiation with 9,10-dimethylbenzanthracene.

Treatment with oleic acid alone did not produce tumours. For classification in one of the categories for carcinogens, the effects of the substance itself are relevant, and only papillomas were found in the only study with positive results (Holsti 1959).

The relevance of mouse skin initiation–promotion experiments was re-assessed by the Commission as regards possible carcinogenic effects in humans on the basis of the present knowledge of the mechanism of action. As the application of oleic acid alone did not produce tumours, and the tumour-promoting effect on the skin of mice only is not considered predictive for the formation of skin tumours in humans (Schwarz et al. 2015), the available data are not reliable enough for the classification of oleic acid in one of the categories for carcinogens, and oleic acid is therefore no longer classified in Category 3A.

**Germ cell mutagenicity.** There are no new data available. As described in the documentation from 2001 (documentation "Oleic acid" 2002), oleic acid is regarded as not genotoxic in vitro; in vivo investigations are not available. As the available long-term studies did not yield evidence of genotoxic effects, the substance is not classified in one of the categories for germ cell mutagens.

**MAK value and peak limitation.** There are no studies available for the effects of inhalation exposure to the irritative oleic acid. As no NOAEC or NOAEL can be derived from the available studies, oleic acid is listed in Section IIb of the List of MAK and BAT Values. Peak limitation is therefore not carried out.

**Prenatal toxicity.** There are no valid studies available for the developmental toxicity of oleic acid. As no MAK value can be derived, it is not possible to classify the substance in one of the pregnancy risk groups.

**Absorption through the skin.** There are, as before, no data available for the absorption of oleic acid through the skin. The skin penetration-enhancing property of oleic acid known from its pharmaceutical application is, in itself, no reason for designation with an "H" (for substances which can be absorbed through the skin). The systemic toxicity is low, as was found in a 2-year drinking water study with female F344-rats, in which no adverse effects were observed after the administration of sodium oleate doses of 2300 mg/kg body weight (documentation "Oleic acid" 2002). All in all, no data are available which would justify designation with an "H".

**Sensitization.** No positive clinical findings are available for a contact sensitization potential of oleic acid. Unequivocal contact sensitization potential cannot be derived for oleic acid from the questionable or borderline positive result in a maximization test and the formally positive findings in a local lymph node assay. There are no data available for sensitization of the airways. Oleic acid is therefore not designated with "Sh" or "Sa" (for substances which cause sensitization of the skin and airways).

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