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Isodecyl oleate

MAK Value Documentation, supplement – Translation of the German version from 2019

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Keywords

isodecyl oleate; lung; accumulation; maximum workplace concentration; MAK value; developmental toxicity; fertility; read-across

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated isodecyl oleate [59231-34-4], considering all toxicological endpoints. Available publications and unpublished study reports are described in detail. As with white mineral oil, inhalation of aerosols of the hardly water-soluble isodecyl oleate could result in overload in the lung, inflammatory reactions and microgranulomas. To prevent this overload, a MAK value of 5 mg/m^3 is derived for the respirable fraction by analogy with white mineral oil and Peak Limitation Category II as well as an excursion factor of 4 are set. A NOAEL for developmental effects is 300 mg/kg body weight and day after oral treatment of rats but no teratogenicity was examined and isodecyl oleate is assigned to Pregnancy Risk Group D. Isodecyl oleate is not genotoxic in bacteria. Carcinogenicity studies carried out according to the test guidelines are not available. There are no indications of a contact sensitizing potential of isodecyl oleate. Skin contact is not expected to contribute significantly to systemic toxicity.

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MAK value (2018)	**5 mg/m³ R (respirable fraction)**
Peak limitation (2018)	**Category II, excursion factor 4**
Absorption through the skin	–
Sensitization	–
Carcinogenicity	–
Prenatal toxicity (2018)	**Pregnancy Risk Group D**
Germ cell mutagenicity	–
BAT value	–
CAS number	59231-34-4
Melting point at 1013 hPa	< –20 °C (ECHA 2017)
Boiling point at 1013 hPa	> 300 °C (ECHA 2017)
Density at 20 °C	0.86 g/cm³ (ECHA 2017)
Vapour pressure at 20 °C	1.7×10^{-10} hPa (calculated; ECHA 2017)
log K_{OW}	12.65 (calculated; Zschimmer & Schwarz 2012 b)
Solubility at 20 °C	2.14×10^{-10} g/l water (calculated; Zschimmer & Schwarz 2012 b)

Metal-working fluid concentrates contain amounts of up to 20% of the substance (Hartwig 2014, available in German only).

Isodecyl oleate belongs to the UVCB substances (**U**nknown or **V**ariable composition, **C**omplex reaction products or **B**iological materials).

The documentation for isodecyl oleate dates from 1998 (Greim 2001). This supplement was prepared on the basis of new studies of repeated administration and reproductive toxicity. It examines whether it is possible to establish a MAK value for isodecyl oleate. To complete the toxicological profile, studies with the structural analogue ***n*-decyl oleate** [3687-46-5] and similar fatty acid esters, such as **2-ethylhexyl oleate** [26399-02-0], **oleyl oleate** [3687-45-4] and **2-octyldodecyl isooctadecanoate** [93803-87-3], are also included. The names of these substances are shown in bold print for clarity.

Toxic Effects and Mode of Action

A study in rats with oral administration of isodecyl oleate for 35 to 56 days did not reveal any substance-related effects in the males and in females that were not pregnant up to the highest dose tested of 1000 mg/kg body weight and day. This value is confirmed by structure–activity comparisons with ***n*-decyl oleate**. However, after gavage administration of isodecyl oleate to female Sprague Dawley rats during mating, pregnancy and lactation, post-implantation losses, stillbirths, not viable offspring and other effects were observed at 1000 mg/kg body weight and day.

Isodecyl oleate is not irritating to the skin or eyes of rabbits.

In guinea pigs and rabbits, isodecyl oleate did not induce skin-sensitization in studies not conducted according to OECD test guidelines. The structurally closely related substance ***n*-decyl oleate** did not induce sensitization in mice.

As studies with the structural analogues ***n*-decyl oleate**, **2-octyldodecyl isooctadecanoate**, **2-ethylhexyl oleate**, **oleyl oleate** or **C16-18 fatty acid isotridecyl ester** did not reveal any genotoxic effects in bacteria or mammalian cells, it can be assumed that isodecyl oleate is likewise not genotoxic.

Studies of its carcinogenicity are not available.

Mechanism of Action

After inhalation exposure, it is conceivable that isodecyl oleate that has entered the lungs is cleaved into oleic acid and isodecyl alcohol. Oleic acid is used in animal experiments as a model substance for the development of the acute respiratory distress syndrome (ARDS) in humans. After intravenous or intratracheal administration of oleic acid or oleic acid suspensions (in albumin or phosphate-buffered saline), for example to rats (Akella et al. 2014; Dickey et al. 1981; Ito et al. 2005), mice (Gonçalves-de-Albuquerque et al. 2012, 2013, 2015), dogs (Henning et al. 1986; Kato et al. 1998; Leeman et al. 1990; Scillia et al. 2001) and pigs (Neumann et al. 2000), lung damage similar to ARDS was induced. ARDS is defined as acute respiratory insufficiency with an initial increase in the permeability of the alveolar and capillary membranes and oedema formation in the alveoli and interstitium (see Gonçalves-de-Albuquerque et al. 2015). However, experiments with intravenous or intratracheal administration are not relevant for occupational exposure. As there are no corresponding inhalation studies with oleic acid, there is no NOAEC for this effect. It is not clear whether oleic acid is released after inhalation of isodecyl oleate. For other fatty acids, there are no studies of occupational exposure available. Pharmaceutical products, such as propellant-driven metered-dose inhalers for the inhalation of drugs in which the active ingredient is suspended, are known to contain dissolved excipients such as oleic acid, sorbitan trioleate or lecithin. The oleic acid serves as a suspension stabilizer (Kircher 2003). Assuming that in a metered-dose aerosol the spray volume is 50 µl (for example Fujisawa 2002; TEVA 2008) and assuming that oleic acid makes up a maximum of 1%, the patient would inhale 0.5 µl of oleic acid in a single application. With 1 to 2 single doses 3 to 4 times a day or 4 sprays twice a day (for example Fujisawa 2002), the patient would inhale about 4 µl oleic acid per day. However, the package inserts of many drugs administered in this way do not describe the symptoms of pulmonary oedema, such as shortness of breath, cyanosis, expectoration and coughing (for example Cheplapharm 2008; Hexal 2016).

Effects in Humans

There are no data available for single or repeated exposures, allergenicity, reproductive toxicity, genotoxicity or carcinogenicity.

Local effects on skin and mucous membranes

There are no data available for the irritating effects on the skin of isodecyl oleate in humans.

On the inside of the forearms of volunteers, 2-hour application of the undiluted structural analogue ***n*-decyl oleate** with a plaster or application for 30 minutes with simultaneous massaging into the skin of the substance with a glass rod every 30 seconds (Burckhardt test) did not cause irritation (Greim 1998).

Animal Experiments and in vitro Studies

Acute toxicity

Inhalation

There are no data available for isodecyl oleate.

Oral administration

In rats, the LD_{50} of isodecyl oleate was greater than 2000 mg/kg body weight (Greim 2001), as was the case with the structural analogue ***n*-decyl oleate** (Greim 1998).

Subacute, subchronic and chronic toxicity

Oral administration

In female Sprague Dawley rats given daily gavage doses of isodecyl oleate of up to 1000 mg/kg body weight and day 2 weeks before mating up to day 3 after giving birth, organ changes were not observed. Only during lactation was there a body weight loss of 9.4%. The toxic effects on development, such as post-implantation losses, stillbirths or dead pups are described in the Section "Developmental toxicity". In male animals, no substance-related damage occurred after the administration of isodecyl oleate doses of up to 1000 mg/kg body weight and day for 35 days (see Table 1). The NOAEL was thus 1000 mg isodecyl oleate/kg body weight and day for the male animals and for females that were not pregnant (Zschimmer & Schwarz 2013). This NOAEL is confirmed by the results with the structural analogue ***n*-decyl oleate** (Greim 1998) (see Table 1).

Tab. 1 Toxicity studies with repeated oral administration of isodecyl oleate and n-decyl oleate

Species	Exposure	Findings	References
Isodecyl oleate			
rats, Sprague Dawley, 5 ♂ and 5 ♀	**14 days**, 0, 100, 300 or 1000 mg **isodecyl oleate** (in corn oil)/kg body weight and day, purity 99%, 7 days/week, gavage	**1000 mg/kg body weight**: **NOAEL**; no effects on body weights, organ weights or after gross-pathological examination of all organs; histopathological examination not carried out	Zschimmer & Schwarz 2012 a
rats, Sprague Dawley, 10 ♂ and 10 ♀	♂: **35 days**, ♀: **max. 56 days**, 0, 100, 300 or 1000 mg **isodecyl oleate** (in corn oil)/kg body weight and day, purity 77,8% (C_{14}–C_{20}, < 10% per component) 7 days/week, gavage, ♂: start 2 weeks before mating, ♀: start 2 weeks before mating up to 3 days after giving birth	**300 mg/kg body weight**: ♀: **NOAEL**; **1000 mg/kg** body weight: ♀: effects on reproduction see Sections "Fertility" and "Developmental toxicity", ♂: NOAEL, no effects on spermatogenesis; blood status, clinical chemistry or blood coagulation: no unusual findings; gross-pathological examination: no effects on tongue, trachea, larynx, oesophagus, gastrointestinal tract, adrenal glands, bone marrow, nervous system, spinal cord, brain, heart, kidneys, ureter, bladder, reproductive organs, liver, lungs, lymph nodes, spleen, thyroid gland; organ weights: no effects on testes, epididymis, kidneys, adrenal glands, brain, heart, liver, spleen, thymus; histopathological examination: no unusual findings	Zschimmer & Schwarz 2013
***n*-Decyl oleate**			
rats, Wistar, 10 treated ♂ and 10 treated ♀, 5 untreated ♂ and 5 untreated ♀	**28 days**, 0, 100, 500 or 1000 mg ***n*-decyl oleate** (in olive oil)/kg body weight and day, purity not specified, 5 days/week, gavage, recovery period: 28 days	**1000 mg/kg body weight**: **NOAEL**; no effects on body weights, organ weights; no gross-pathological and histological changes	Greim 1998

Summary: From the studies with repeated oral administration to Sprague Dawley rats, a NOAEL of 1000 mg isodecyl oleate/kg body weight and day was obtained in females that were not pregnant and in the males due to the lack of effects at the highest dose tested. This value is confirmed by the findings for the structurally similar ***n*-decyl oleate**.

Dermal application

There are no data available for isodecyl oleate.

Local effects on skin and mucous membranes

Skin

In various studies of the irritant effects of undiluted isodecyl oleate on the skin of rabbits, mean irritation indices of 0, 0.13, 0.28 or 1.0 were found (Greim 2001). Thus, isodecyl oleate is not regarded as irritating to the skin.

In rabbits, ***n*-decyl oleate** was very slightly irritating (no other details) (Greim 1998).

Eyes

In rabbits, the instillation of a 15% isodecyl oleate solution resulted in an average irritation score of 0.3 (< 0.5 not irritating to 2.0 slightly irritating; ECHA 2017) while the value for the undiluted substance was reduced from 4 after one hour to 0 after 24 hours (Greim 2001).

Also other fatty acid esters, such as **2-ethylhexyl laurate**, **isooctadecyl palmitate** and **2-octyldodecyl isooctadecanoate**, were not irritating to the eyes (ECHA 2017).

Summary

Isodecyl oleate is not irritating to the skin and eyes of rabbits.

Allergenic effects

In an earlier study not carried out according to the test guidelines in 10 guinea pigs with intradermal injection of 15% isodecyl oleate and in a 60-day open patch test in groups of 3 rabbits with 15% or undiluted isodecyl oleate, no evidence of sensitization was found (Greim 2001). However, the results are not suitable for inclusion in the evaluation.

A local lymph node assay (LLNA) carried out according to OECD Test Guideline 429 in female CBA/J mice with 25%, 50% and 100% of the structurally very similar ***n*-decyl oleate** in acetone/olive oil (4:1) yielded stimulation indices of 1.17, 1.95 and 2.08, respectively, and thus a clearly negative result (ECHA 2017).

Reproductive and developmental toxicity

Fertility

In a study carried out according to OECD Test Guideline 422, groups of 10 male and 10 female Sprague Dawley rats were given gavage doses of isodecyl oleate of 0, 100, 300 or 1000 mg/kg body weight and day starting 2 weeks before mating. In the males, the daily treatment was carried out for 35 days, in the females up to 3 days after giving birth (see also the Section "Subacute, subchronic and chronic toxicity") for a maximum of 56 days. Isodecyl oleate did not affect the reproductive organs, spermatogenesis and the number of corpora lutea (Zschimmer & Schwarz 2013).

Summary: The NOAEL for effects on fertility in Sprague Dawley rats is 1000 mg isodecyl oleate/kg body weight and day.

Developmental toxicity

In a study carried out according to OECD Test Guideline 422, groups of 10 male and 10 female Sprague Dawley rats were given gavage doses of isodecyl oleate of 0, 100, 300 or 1000 mg/kg body weight and day, starting 2 weeks before mating. In the males, daily treatment lasted for 35 days, in the females up to 3 days after giving birth, for a maximum of 56 days (see also the Section "Subacute, subchronic and chronic toxicity"). The males tolerated isodecyl oleate doses of up to 1000 mg/kg body weight and day and the females up to 300 mg/kg body weight and day without substance-related effects. At 1000 mg isodecyl oleate/kg body weight and day, post-implantation losses were increased in the females (21.7%, control animals 7.6%), and a 24.4% reduction in total litter weights compared with the value in the control animals and 9 stillbirths (none in the control group) were found. During lactation, the body weights of the dams were reduced by 9.4%. 4 days after giving birth, 2 dams had only dead pups: in one case, 3 pups died immediately after birth and 7 were eaten by the mother. In the other case, none of the 11 pups had consumed milk. A total of 30 pups from 3 of the treated dams died, compared with 5 pups from 10 control animals. Only in the 3 animals with dead pups was the feed intake reduced (by 42% to 72%). The authors considered the complete loss of offspring in 2 of 7 dams to be substance-related (Zschimmer & Schwarz 2013).

Summary: The NOAEL for developmental toxicity in Sprague Dawley rats is 300 mg isodecyl oleate/kg body weight and day. At 1000 mg isodecyl oleate/kg body weight and day, there was an increased incidence of post-implantation losses, stillbirths and not viable offspring.

Genotoxicity

In vitro

There are no data available for isodecyl oleate.

Investigations with structural analogues (see Table 2), such as ***n*-decyl oleate**, **2-octyldodecyl isooctadecanoate**, **2-ethylhexyl oleate**, **oleyl oleate** or **C16-18 fatty acid isotridecyl ester**, did not reveal genotoxic effects in bacteria or mammalian cells (ECHA 2017).

Tab. 2 Genotoxicity of n-decyl oleate and structural analogues in vitro

End point	Test system	Concentration [µg/plate][a)]	Effective concentration[a)]	Cytotoxicity[a)]	Results		References
					–m. a.	+m. a.	
***n*-Decyl oleate**							
gene mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	4–2500	–	–	–	–	Henkel 1979
2-Octyldodecyl isooctadecanoate							
gene mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537, Escherichia coli WP2 uvr A	0, 10, 33, 100, 333 or 1000	–	–	–	–	ECHA 2017
CA	human lymphocytes	0, 333 or 1000 µg/ml	–	–	–	–	ECHA 2017
2-Ethylhexyl oleate (purity > 60%)							
CA	human lymphocytes	0, 3, 10 or 33 µg/ml	–	33 µg/ml precipitation	–	–	ECHA 2017

Tab. 2 *(continued)*

End point	Test system	Concentration [µg/plate][a)]	Effective concentration[a)]	Cytotoxicity[a)]	Results		References
					–m. a.	+m. a.	
gene mutation $TK^{+/-}$	mouse lymphoma L5178Y cells	0.03, 0.1, 0.3, 1, 3, 10, 33 or 100 µg/ml	–	≥ 333 µg/ml precipitation	–	–	ECHA 2017
Oleyl oleate (no other details)							
CA	V79 cells	0, 10, 60 or 100 µg/ml	–	> 100 µg/ml precipitation	–	–	ECHA 2017
gene mutation HPRT	V79 cells	10, 30, 60 or 100 µg/ml	–	> 100 µg/ml precipitation	–	–	ECHA 2017
C16–18 fatty acid isotridecyl ester							
gene mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	8, 40, 200, 1000 or 5000	–	–	–	–	ECHA 2017

[a)] Values given are in µg/plate unless indicated otherwise
CA: chromosomal aberration; HPRT: hypoxanthine phosphoribosyl transferase; –m. a.: without metabolic activation; +m. a.: with metabolic activation

In vivo

There are no data available for isodecyl oleate.

Groups of 5 male and 5 female Swiss CD1 mice were given single intraperitoneal injections of **2-octyldodecyl isooctadecanoate** (in corn oil) of 0, 500, 1000 or 2000 mg/kg body weight. Examination of the bone marrow cells after 24 or 48 hours did not reveal an increased incidence of micronuclei. The ratio between polychromatic and normochromatic cells was not significantly changed (ECHA 2017).

Conclusion

As investigations with the structural analogues ***n*-decyl oleate**, **2-octyldodecyl isooctadecanoate**, **2-ethylhexyl oleate**, **oleyl oleate** or **C16-18 fatty acid isotridecyl ester** did not yield genotoxic effects in bacteria or mammalian cells, and micronuclei were not induced in the bone marrow of mice with **2-octyldodecyl isooctadecanoate**, it can be assumed that also isodecyl oleate is not genotoxic.

Carcinogenicity

There are no data available for isodecyl oleate.

Manifesto (MAK value/classification)

The critical effect is the assumed accumulation of the substance in the lungs due to its poor solubility in water.

MAK value. Suitable studies in humans or inhalation studies in animals are not available for evaluation.

In a study carried out according to OECD Test Guideline 422 in Sprague Dawley rats that had been given a gavage dose of 1000 mg isodecyl oleate/kg body weight and day for a maximum of 56 days 2 weeks prior to mating until 3 days after giving birth, a body weight loss of 9.4% was observed only during the lactation period. At 1000 mg isodecyl oleate/kg body weight and day, post-implantation losses (21.7%, control animals 7.6%) were increased, total litter weights were reduced by 24.5%, and 9 stillbirths (none in the control group) were observed; 4 days after birth, 30 pups had died in 3 treated mothers (a total of 5 in 10 controls). This results in a NOAEL of 300 mg/kg body weight and day.

The following toxicokinetic data are taken into consideration for the extrapolation of this NOAEL to a concentration in workplace air: the daily exposure of the animals compared with the 5 days per week exposure at the workplace (7:5), the species-specific toxicokinetic correction value for the rat (1:4), the body weight (70 kg) and respiratory volume (10 m^3) of the person, and the assumed 100% inhalation and oral absorption. The concentration calculated from this is 735 mg isodecyl oleate/m^3. Taking into account a possible increase in effects over time and the extrapolation of data from experimental studies with animals to humans (1:2 in each case) and using the "preferred value approach", a MAK value of 100 mg isodecyl oleate/m^3 I (inhalable fraction) would be derived due to the maternal toxicity. However, this value cannot be used for inhalation exposure, because as soon as isodecyl oleate is inhaled, it most likely accumulates in the lungs due to its poor solubility in water, as is the case with pharmaceutical white mineral oil. Because of the expected lung toxicity, a MAK value of 5 mg/m^3 R (respirable fraction) has been set for isodecyl oleate in analogy to that for pharmaceutical white mineral oil.

Peak limitation. In analogy to white mineral oil, which, due to its cumulative, late-onset effect, is assigned to Peak Limitation Category II with an excursion factor of 4, isodecyl oleate has likewise been assigned to Peak Limitation Category II with an excursion factor of 4.

Absorption through the skin. Quantitative data for the absorption of the substance through the skin are not available. Model calculations are not permitted due to its extremely poor solubility in water and especially due to the extremely high log K_{OW}. Isodecyl oleate is therefore not designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Allergenic effects. There are no clinical or experimental data indicating a skin sensitization potential of isodecyl oleate. A valid local lymph node assay in mice with the structurally very similar ***n*-decyl oleate** yielded a negative result. There are no data for respiratory sensitization, so that isodecyl oleate is not designated with either "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

Prenatal toxicity. In an oral study in rats with gavage administration of isodecyl oleate for a maximum 56 days starting 2 weeks prior to mating until 3 days after giving birth, NOAELs of 300 mg/kg body weight and day were obtained for maternal and developmental toxicity. After toxicokinetic conversion (see above) this value corresponds to a concentration in workplace air of 735 mg/m^3. As there are no studies of teratogenicity and the available data are not sufficient for a final evaluation, isodecyl oleate has been assigned to Pregnancy Risk Group D.

Germ cell mutagenicity and carcinogenicity. There are no data available for the carcinogenicity and genotoxicity of isodecyl oleate in vitro and in vivo. Since investigations with the structural analogues ***n*-decyl oleate**, **2-octyldodecyl isooctadecanoate**, **2-ethylhexyl oleate**, **oleyl oleate** or **C16-18 fatty acid isotridecyl ester** did not reveal genotoxic effects in bacteria or mammalian cells, and micronuclei were not induced in the bone marrow of mice treated with **2-octyldodecyl isooctadecanoate**, it can be assumed that also isodecyl oleate is not genotoxic in these test systems. Therefore, the substance is not classified in one of the categories for carcinogens or germ cell mutagens.

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (https://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/conflicts_interest/index.html) ensure that the content and conclusions of the publication are strictly science-based.

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