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Triglycerides (lard oil, palm oil, rapeseed oil, soybean oil)

MAK Value Documentation – Translation of the German version from 2022

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

1 *Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Institute of Applied Biosciences, Department of Food Chemistry and Toxicology, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Building 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)*

Keywords

triglycerides; lung toxicity; overload; inflammation; microgranuloma; MAK value; maximum workplace concentration; aerosol; developmental toxicity; read-across

Abstract

The German Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) summarized and evaluated the data for oils consisting of triglycerides (lard oil [8016-28-2], palm oil [8002-75-3], rapeseed oil [8002-13-9], soybean oil [8001-22-7]) to derive an occupational exposure limit value (maximum concentration at the workplace, MAK value) considering all toxicological end points. Relevant studies were identified from a literature search. The term "triglycerides" refers to mixtures of fatty acid triglycerides, i.e. oily extracts of plant or animal origin. These mixtures are all UVCB substances (substances of Unknown or Variable composition, Complex reaction products or Biological materials). As in the case of white mineral oil, inhalation of the aerosol of poorly water-soluble triglycerides may result in lung overload, inflammatory reactions and microgranulomas. To prevent these overload effects, a MAK value of 5 mg/m^3 has been derived for the respirable fraction in analogy to white mineral oil and Peak Limitation Category II with an excursion factor of 4 has been set. There are no prenatal developmental toxicity studies of triglycerides that were carried out according to valid test guidelines. The expected levels of intake after inhalation and dermal exposure to triglycerides at the MAK value of 5 mg/m^3 are several orders of magnitude lower than the levels after dietary intake and remain below the recommended daily intake for fats, one of the main components of human nutrition. On the basis of their structure, the fatty acids that form as the degradation products are not expected to induce teratogenic effects. Secondary effects on the foetus due to maternal hypoxia caused by a lung overload are not expected when the MAK value of 5 mg/m^3 is observed. Therefore, triglycerides have been assigned to Pregnancy Risk Group C. Triglycerides are not genotoxic. Rapeseed oil did not induce tumours in a carcinogenicity study in rats at a dose of 4100 mg/kg body weight and day. The chemical structures of the triglycerides do not raise concerns of a carcinogenic potential. Refined triglycerides show no indication of a sensitizing potential. Crude unrefined rapeseed oil and soybean oil need to be evaluated separately as their sensitizing potential may be influenced by significantly higher levels of proteins. Skin contact is not expected to contribute significantly to systemic toxicity.

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MAK value (2021)	**5 mg/m³ R (respirable fraction)**
Peak limitation (2021)	**Category II, excursion factor 4**
Absorption through the skin	–
Sensitization	–
Carcinogenicity	–
Prenatal toxicity (2021)	**Pregnancy Risk Group C**
Germ cell mutagenicity	–
BAT value	–

	lard oil	palm oil	rapeseed oil	soybean oil
Synonyms	–	palm butter	colza oil	soya oil
CAS number	8016-28-2	8002-75-3	8002-13-9	8001-22-7
Molecular formula	no data	no data	no data	no data
Molar mass	no data	no data	no data	no data
Melting point (°C)	–2 (ChemicalBook 2020 a; NCBI 2021 a)	27–42.5 (NCBI 2021 b), 25–50 (Burnett et al. 2017)	–30.6 to –12.0 (EFSA 2013), –10 to –2 (IFA 2018)	22–31 (NCBI 2021 c)
Boiling point (°C)	no data	no data	> 350 (no data for pressure; EFSA 2013; IFA 2018)	no data
Density (g/cm³)	0.905–0.915 (no data for temperature; ChemicalBook 2020 a)	0.89–0.92 at 50 °C/25 °C (NCBI 2021 b)	0.913–0.917 at 20 °C (IFA 2018)	0.917 (no data for temperature; ChemicalBook 2020 b), 0.916–0.922 (no data for temperature; NCBI 2021 c)
Vapour pressure (hPa)	no data	no data	1.33×10^{-20} at 20 °C (calculated) (EFSA 2013) < 1 at 20 °C (IFA 2018)	no data
log K_{OW}	no data	no data	23.2908 (calculated) (EFSA 2013)	no data
Solubility (mg/l water)	no data	insoluble in water (NCBI 2021 b)	2.551×10^{-20} (calculated) (EFSA 2013)	insoluble in water (NCBI 2021 c)

	lard oil	palm oil	rapeseed oil	soybean oil
Hydrolytic stability: saponification value (mg potassium hydroxide/g fat)	no data	245–255 (Burnett et al. 2017) 230–254 (DGF n.d.)	168–192 (Burnett et al. 2017) 168–181 (DGF n.d.)	188–195 (DGF n.d.) 189–195 (DGF n.d.)
Stability	Lard oil may oxidize on contact with air and become rancid.	Palm oil may oxidize on contact with air and become rancid.	Rapeseed oil may oxidize on contact with air and become rancid.	Soybean oil may oxidize on contact with air and become rancid.
Production	Lard is melted, then crystallized or grained at 7 °C (lard) and pressed (The Editors of Encyclopaedia Britannica 2018).	Palm oil is obtained from the fruit of the palm tree (Elaeis guineensis) by pressing and centrifuging. The production process involves the inactivation of lipases by steam followed by the separation of the fruit from the palm bunches in preparation for pressing. Solids and moisture are removed from the extracted oil by centrifugation and further drying under vacuum (Johnson 2000).	The seeds of the oilseed rape plant (Brassica napus) are reduced in size ("flaking") using rollers followed by conditioning, or heating to a defined water content, and the actual pressing process. A refining process is required for the production of pure rapeseed oil. Depending on the quality of the final product, this is followed by vacuum drying, bleaching, neutralization and deodorization (Bickel 2012).	Obtained from soybeans (Glycine max.) by solvent extraction using petroleum hydrocarbons or, to a lesser extent, by pressing using continuous screw-press operations (US EPA 1993).
Purity	no data	no data	no data	no data
Impurities	no data	no data	maximum erucic acid content: 2% (EFSA 2013)	no data

	lard oil	palm oil	rapeseed oil	soybean oil
Uses	Constituent of lubricants, used in cutting oils, soap manufacture (The Editors of Encyclopaedia Britannica 2018), for the production of oiling wool, antibiotic fermentation, antifoam agents (NCBI 2021 a), lard glycerides: constituent of cosmetic products (CIREP 2001)	Food, constituent of cosmetic products, soap manufacture, pharmaceuticals, lubricants for cutting tools, hot-dipped tin coatings, as a plasticizer in rubber processing, in cotton-goods finishing, as a substitute for tallow as a mould-release agent (NCBI 2021 b), in crayon and candle production, tin plate industry (Burnett et al. 2017)	Food, biodegradable oils and lubricants, as a base for paints and varnishes, for the production of plasticizers, surfactants and pesticides, as a fuel or fuel additive in the form of unprocessed oil or rapeseed methyl ester (biodiesel) (Fachagentur Nachwachsende Rohstoffe 2005)	Base for paints and varnishes (oils with a high drying rate), plasticizers and lubricating oil (Fachagentur Nachwachsende Rohstoffe 2005), insecticides and miticides for citrus fruits and a large variety of ornamental plants, food (US EPA 1993)
Maximum concentration used in metal working fluid concentrates (Hartwig and MAK Commission 2018, available in German only)	50%	50%	100%	20%

General description of the group of triglycerides

The term ‘triglycerides’ is used to refer to oils extracted from plants and animals that are made up of fatty acid triglycerides. These oils are all classified as substances of unknown or variable composition, complex reaction products or biological materials (UVCB substances).

The current list of constituents of metal-working fluids, hydraulic fluids and other lubricants (Hartwig and MAK Commission 2018) includes a number of vegetable and animal-based oils. The oils below are oils from this list that contain fatty acid triglycerides:

- coconut oil (CAS number: 8001-31-8)
- lard oil (CAS number: 8016-28-2)
- palm oil (CAS number: 8002-75-3)
- rapeseed oil (CAS number: 8002-13-9)
- castor oil (CAS number: 8001-79-4)
- soybean oil (CAS number: 8001-22-7)
- sperm oil (CAS number: 68991-30-0)

Tall oil is not a fatty acid triglyceride of plant or animal origin because it is made up of fatty and resin acids and not triglycerides. Another oil that has not been included in the list is **jojoba oil** because it is almost entirely made up of waxes of long-chain fatty acids with alcohols and hardly any triglycerides. **Sperm oil** has been moved to the ‘historical list’ (Hartwig and MAK Commission 2018) because the oil is no longer used for metal-working fluids.

Unlike other fatty acid triglycerides, **castor oil** was found to cause severe irritation of the skin and eyes of rabbits in 1 study and slight irritation in another study as well as slight irritation of the skin of guinea pigs (CIREP 2007). The primary constituent of castor oil (87% to 90%) is the triglyceride of ricinoleic acid, a fatty acid with a hydroxy group at the twelfth carbon atom. The chemical structure of ricinoleic acid is similar to that of prostaglandin E1, but they do not have the same physiological properties. Castor oil and ricinoleic acid were not found to have a marked sensitizing potential in case studies and animal studies. However, positive reactions to both substances were obtained in some cases, particularly from patients with intolerance reactions to lip care products. For example, in one study, 29 (2 men, the rest women) of a total of 202 patients with cheilitis (182 women, 20 men) who had presented themselves at a clinic in Singapore between January 1996 and December 1999 produced positive reactions to ricinoleic acid in the patch test (no other details) (Lim and Goh 2000). Castor oil is derived from the seeds of the castor bean (Ricinus communis) by cold pressing and, in some cases, subsequent clarification of the oil by heat. Castor oil does not contain the highly toxic ricin, a constituent of the seeds (CIREP 2007). Castor oil has not been included in this group evaluation because of the local irritant effects.

The common properties of all of the triglyceride mixtures that are evaluated together in this documentation are that they tend to be viscous oils with a low vapour pressure. Exposure is expected to occur only in the form of an aerosol. These oils all cause no or at most slight irritation of the skin and eyes (see Section 5.3) and are systemically toxic after oral administration only at doses of several grams per kilogram body weight (see Section 5.2.2).

The data for **coconut oil** are available in a separate evaluation (Hartwig and MAK Commission 2020).

Composition

Rapeseed oil is composed mainly of triglycerides containing the fatty acids oleic acid (18:1, number of carbon atoms : number of double bonds; 51.0% to 70.0%), linoleic acid (18:2; 15.0% to 30.0%), linolenic acid (18:3; 5.0% to 14.0%), palmitic acid (16:0; 2.5% to 7.0%) and gadoleic acid (20:1; 0.1% to 4.3%). It contains other fatty acids in amounts with a maximum percentage by weight of less than 2% (DGF 2018) and has a maximum erucic acid content (22:1, (13*Z*)-13-docosenoic acid; double bond between carbon atoms 13 and 14) of 2% (EFSA 2013). Up to the 1970s, erucic acid made up about 40% of the total fatty acids that occurred in wild varieties of rapeseed. The varieties that have been cultivated since then contain 0.5% erucic acid. To account for the reversible myocardial lipidosis that was induced in animals and humans by erucic acid, a safety factor of 100 was applied to derive a TDI (tolerable daily intake) value for erucic acid of 7 mg/kg body weight and day (EFSA Panel on Contaminants in the Food Chain (CONTAM) et al. 2016). The rapeseed oils that are used for lubricants may contain higher levels of erucic acid than are permissible for foods.

Palm oil is composed mainly of triglycerides containing the fatty acids palmitic acid (39.9% to 47.5%), oleic acid (36.0% to 44.0%), linoleic acid (9.0% to 12.0%), stearic acid (18:0; 3.5% to 6.0%) and myristic acid (14:0; 0.5% to 2.0%). Other fatty acids each have a maximum weight content of less than 2% (DGF 2018).

Soybean oil is composed mainly of triglycerides containing the fatty acids linoleic acid (48.0% to 59.0%), oleic acid (17.0% to 30.0%), linolenic acid (4.5% to 11.0%), palmitic acid (8.0% to 13.5%) and stearic acid (2.0% to 5.4%). Other fatty acids each have a maximum weight content of less than 2% (DGF 2018).

Lard oil is composed mainly of triglycerides containing the fatty acids oleic acid (35.0% to 55.0%), palmitic acid (20.0% to 30.0%) and stearic acid (8.0% to 22.0%). Other constituents are triglycerides containing linoleic acid (4.0% to 12.0%) and palmitoleic acid (16:1; 2.0% to 4.0%). Other fatty acids each have a maximum weight content of less than 1.5% (DGF 2018).

Data for fatty acids

Documentation for oleic acid was published in 1998 (Greim 2002) followed by a supplement in 2016 (Hartwig and MAK Commission 2017 a). Documentation for myristic acid, palmitic acid and stearic acid is available (Greim 1999, available in German only).

The present documentation includes data for oleic acid in some sections because oils such as rapeseed oil are composed of between 51.0% and 70.0% oleic acid (as a triglyceride constituent). Oleic acid may be the cause of any systemic effects induced by rapeseed oil because, after oral uptake of rapeseed oil, the triglycerides are cleaved by pancreatic lipase in the duodenum, forming and subsequently being taken up as fatty acids, glycerol as well as mono and diacylglycerides.

Mist formation

Studies of impaction and centrifugal forces found that, in comparison with petroleum-based emulsions, vegetable oil-based emulsions produced slightly more mist by impaction and slightly less mist by centrifugal force. In studies of evaporation and recondensation, vegetable oil-based emulsions produced 30% to 90% less mist than the mineral oils (Raynor et al. 2005).

1 Toxic Effects and Mode of Action

Animal studies with administration of triglycerides in oral doses in the gram/kg body weight range revealed changes typical of increased fat intake. In rats, for example, the changes included increased free cholesterol and triglyceride levels in the plasma in addition to histological changes in the liver such as vacuolization of the hepatocytes, lipid accumulation and focal necrosis. In addition, rats and mice became obese and had shortened lifespans. In rabbits, increased cholesterol and triglyceride levels in the plasma and increased blood pressure were observed in this dose range.

Inhalation studies are not available for individual triglycerides. In analogy to the effects after exposure to white mineral oil, exposure to triglyceride aerosols is expected to lead to macrophage accumulation and the formation of microgranulomas in the lungs.

Triglycerides cause no or at most minimal irritation of the skin and eyes.

There is no evidence that triglycerides induce sensitizing effects on the skin or airways. Relevant findings are not available for lard and palm oil or for (fully) refined rapeseed and soybean oils.

No evidence for toxic effects on reproduction or teratogenicity was obtained for any of the substances.

The triglycerides do not have a genotoxic potential.

In a carcinogenicity study with male Wistar rats, carcinogenic effects were not observed in animals given refined rapeseed oil with the feed at an average dose of 4100 mg/kg body weight and day.

2 Mechanism of Action

Fatty acid triglycerides are hydrolysed in the organism. Hydrolysis is catalysed by lipases and leads to the cleavage of the ester bond, forming fatty acids and diglycerides, monoglycerides and glycerol.

Lipases are produced in the stomach, pancreas, small intestines and adipose tissue. They occur also in the alveolar macrophages in the lungs. There are lipoprotein lipases (Camps et al. 1991; Mahoney et al. 1982; Okabe et al. 1984), phospholipid lipases (Errasfa 1991), triacylglyceride lipases (Khoo et al. 1984; Radovic et al. 2012) and diacylglyceride/2-monoacylglyceride lipases (Errasfa 1991). Interstitial macrophages induce only phagocytosis and cannot degrade mineral oils (Eckert and Jerochin 1981). In theory, lipolytic activity in the lungs is possible outside of the alveolar macrophages, but is probably of subordinate importance.

Mineral oil taken up by inhalation has been found to undergo phagocytosis and degradation by the alveolar macrophages (Eckert and Jerochin 1981). Incomplete phagocytosis by alveolar macrophages induces inflammatory reactions (exogenous lipoid pneumonia), microgranulomas and even fibrotic changes (SCOEL 2011).

Mechanistically, the changes induced by mineral oil in the lungs can be explained by overloading caused by accumulation in the alveolar macrophages (Hartwig and MAK Commission 2019). As a mixture of primarily saturated hydrocarbons, mineral oil cannot undergo hydrolysis because it does not contain hydrocarbons with ester groups.

Also for the triglycerides evaluated in this documentation, it is to be assumed that they accumulate in the alveolar macrophages after being taken up by inhalation from oil mists. The triglycerides, however, are then hydrolysed there by lipases.

If the hydrolysis capacity of the lipases is exceeded, this could lead to an overload with the corresponding consequences. In contrast to mineral oil, however, it is unclear at which concentration of fatty acid triglycerides an overloading effect can be expected.

A study in mice found that after a single exposure by inhalation to an oil mist (average mass median diameter 2.5 µm) from vegetable and animal oils (corn oil, arachis oil, cod liver oil) for 2 hours, the concentration of oil droplets in the lungs (determined immediately after exposure, the same for all oils) decreased steadily until only a residual amount remained after 4 days (no quantitative data available). By contrast, the concentration of droplets in the lungs from mineral oils (liquid petrolatum and motor oil) remained unchanged from the initial levels after 4 days. When the exposure period was prolonged to 14 to 30 days (5–8 hours/day, 5 days/week, 12 600, 10 600 and 11 200 mg/m^3, respectively), the residual concentrations of vegetable and animal oil droplets were lower than the concentrations of mineral oil droplets (Shoshkes et al. 1950). Both of these findings support the use of analogous findings for mineral oil/white mineral oil as a 'worst case' scenario.

As described above, monoglycerides and diglycerides are produced by lipases in the alveolar macrophages (Camps et al. 1991; Errasfa 1991; Khoo et al. 1984; Okabe et al. 1984). Due to their chemical structures, they are ascribed detergent and surfactant-like properties.

Detergents or emulsifying agents modify the surface tension of the surfactants in the lungs and disrupt the recycling of surfactants. Pulmonary surfactant, as a surface-active protective system, consists mainly of phospholipids and is therefore highly insoluble in water. Lipid metabolism must be very efficient to maintain surfactant homeostasis. Surfactant is recycled and degraded by alveolar macrophages and secreted by type II pneumocytes (Schulz 2017). The high specificity of surfactant recycling and the functionality of the surfactant (maintaining breathing and preventing alveolar collapse) (Schleh and Hohlfeld 2009; Sunde et al. 2017) make it unlikely that triglycerides would disrupt surfactant recycling.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

3.1.1 Triglycerides in general

There are no data for exposure by inhalation or through the skin. After oral uptake, triglycerides in the duodenum are cleaved by pancreatic lipase into fatty acids, glycerol and monoacylglycerides or diacylglycerides and taken up into the enterocytes. It is generally assumed that the chain length of the fatty acids has an effect on oral absorption. While free fatty acids with a chain length of 14 or more carbon atoms (oleic acid, linoleic acid, linolenic acid, palmitic acid, gadoleic acid, stearic acid, myristic acid, palmitoleic acid) are re-esterified to form triglycerides in the enterocytes, free fatty acids with a chain length of 8 to 12 carbon atoms reach the liver directly via the portal vein (Roche and Clark 1994). In serum, the triglycerides are bound to lipoproteins or transported as chylomicrons via the lymphatic system and stored in fatty tissue. Free fatty acids, which are released from the fatty tissue, are either bound to serum albumin or remain in the blood as non-esterified fatty acids. The physiological concentration of free fatty acids in blood plasma is 10 to 300 mg/l. The enteral absorption of free fatty acids decreases with increasing chain length (Greim 1999).

3.1.2 Individual triglycerides

Erucic acid (constituent of **rapeseed oil** triglycerides) and its metabolite as well as gadoleic acid were found in the serum of 70 railway workers and in the fatty tissue and myocardium of 16 deceased persons in Italy who had died of various causes. In 40 of 70 railway workers, erucic acid made up 0.3% to 3.8% of the total fatty acids in serum. Erucic acid levels of 0.3% to 6.8% and gadoleic acid levels of 1.1% to 4.9% were detected in the fatty tissue of the 16 deceased persons. The myocardium of only 14 deceased persons was examined; values over the detection limit were found for erucic acid (0.2% to 2.2%) in 13 samples and for gadoleic acid in 9 samples (no other details; Gatti and Michalek 1975).

After oral administration, rapeseed oil was absorbed by rats more slowly than other fats and oils (no other details; Borg 1975). Groups of 10 female mice were given rapeseed oil by gavage for 3 days (52% erucic acid; 7.4% gadoleic acid) at a level equivalent to 50% of the calories ingested daily. The control animals were fed arachis oil according to the same regimen. Both fatty acids were found to make up about 10% of the total fatty acid composition of the heart and liver and a far smaller fraction was recovered in the skeletal muscles and kidneys (Gatti and Michalek 1975).

There are no studies available for the elimination and half-life of any of the triglycerides.

3.2 Metabolism

After oral uptake, triglycerides in the duodenum are cleaved by pancreatic lipase into fatty acids, glycerol and monoacylglycerides or diacylglycerides (Roche and Clark 1994). In lipid metabolism, the breakdown of fatty acids takes place via successive β-oxidation of the respective terminal C2 unit as the acetic acid thioester of coenzyme A. To a lesser extent, the breakdown of fatty acids can take place in the liver also via ω-oxidation and in the brain via α-oxidation. In the form of their triglycerides, fatty acids are natural components of vegetable and animal fats (neutral fats) and are subject to general fatty acid metabolism (Greim 1999).

Studies with rats revealed that the erucic acid found in rapeseed oil follows different metabolic pathways in the liver (mainly conversion to stearic acid followed by export into neutral lipids) and heart (mainly incorporation into triglycerides). As peroxisomes lack short-chain acyl-CoA oxidase, erucoyl-CoA is not completely degraded in these organelles. Only a single or a few β-oxidation cycles take place, forming mainly gadoleic acid and oleic acid. However, the fatty acids may undergo further β-oxidation in the mitochondria (EFSA Panel on Contaminants in the Food Chain (CONTAM) et al. 2016).

4 Effects in Humans

4.1 Single exposures

There are no data available.

4.2 Repeated exposure

In healthy persons, fresh **palm** and **soybean oils** increase the triglyceride concentrations in plasma. However, the cholesterol levels in persons with palm oil-based diets were lower than the levels found in persons with soybean oil-based diets. This is attributed to the presence of tocotrienols (forms of vitamin E) in palm oil. The findings of epidemiological studies revealed that persons who consume palm oil have a higher likelihood of cardiac arrest than persons who consume soybean oil (NCBI 2021 b).

Preterm babies died after parenteral administration of emulsions containing soybean oil. At autopsy, an intravascular accumulation of fat in the lungs was found (no other details; NCBI 2021 c).

Four young men who ingested 30 g of **lard** daily for 7 days were found to have increased total cholesterol and decreased HDL cholesterol levels in serum and higher HDL cholesterol and HDL phospholipid fractions in serum (no other details; CIREP 2001).

4.3 Local effects on skin and mucous membranes

In clinical studies, petrolatum containing 15% **palm oil** and cosmetic formulations containing 1% to 2% palm oil were not found to cause irritation of the skin (no other details; Burnett et al. 2017).

When used in cosmetics, 39% hydrogenated **soybean oil** in lipstick and 0.19% unsaponifiable fraction of soybean oil in a face and neck care product did not cause irritation of the skin (Burnett et al. 2017).

4.4 Allergenic effects

4.4.1 Sensitizing effects on the skin

No case studies were found that provided evidence of the induction of skin sensitizing effects by pure triglycerides or the oils evaluated in this documentation. Furthermore, topical application of the oils was not reported to cause protein contact dermatitis.

A secondary source referred to a modified Draize test that was used to investigate the sensitizing effects of 15% **palm oil** in petrolatum via occlusive application. After induction treatment for 4 weeks (3 applications a week, each lasting 48 hours) and 12 days without exposure, the challenge was carried out in the form of exposure for 48 hours. The readings taken 46 and 96 hours after the end of treatment did not reveal positive reactions in any of the 110 study participants (Johnson 2000). The REACH registration dossiers for several of the oils include human repeated insult patch tests, each carried out with 88 test persons, that yielded negative results. It is unclear whether these tests were carried out with different collectives or with the same test persons. Paraffinum liquidum (white mineral oil) was used as the vehicle for all of the tests. The test oils were referred to as palm oil (50%) and partially hydrogenated palm oil (75%), partially hydrogenated, high erucic acid rapeseed oil (50%) and partially hydrogenated soybean oil (50%); no other information was provided (ECHA 2013). The results of the tests with the modified oils are not relevant for the evaluation.

Sensitizing effects were not observed in human repeated insult patch tests carried out with 108 and 50 test persons, respectively, for a skin cream containing 39% hydrogenated **soybean oil** (in addition to 12% hydrogenated olive oil) and a lipstick containing only 0.19% unsaponifiable fraction of soybean oil (Burnett et al. 2017). In another human repeated insult patch test, semi-occlusive application of a baby oil containing 5% hydrogenated rapeseed oil did not induce sensitizing effects in 105 test persons (Burnett et al. 2017). Negative results were obtained in repeated insult patch tests with various cosmetic products containing 1% to 2% palm oil as well as in a study of photocontact sensitization with application of a 4% formulation (Johnson 2000). However, these results cannot be used for the evaluation because the oils were tested in modified form and in low concentrations.

There are no studies available that investigated the skin sensitizing effects of **lard oil**.

4.4.2 Sensitizing effects on the airways

There are no data for sensitizing effects on the airways induced by triglycerides or the evaluated oils that contain triglycerides. The findings for the effects on the airways are limited to studies of the effects induced by the proteins contained in the seeds of the rapeseed plant or in soybeans. In addition, there are several immunological studies that investigated possible immunological gastrointestinal intolerances after oral administration of rapeseed or soybean oil.

4.4.2.1 Rapeseed oil

A total of 5 cases of occupational sensitization of the airways were reported including 2 animal feed production workers (Monsalve et al. 1997; Suh et al. 1998) and 3 farmers (Alvarez et al. 2001) that were induced by exposure to the rapeseed protein during the production or handling of feed. In an immunoblot analysis of rapeseed extracts using the serum of one of the feed production workers, 14 reactive bands were detected in the range from 10 kDa to 160 kDa; however, these were not attributed to any specific proteins (Suh et al. 1998). In a second worker, an immunoblot assay with 3 purified protein fractions (2S albumins, napin) from rapeseed produced bands at 14/16 kDa. Additional bands at 30 and 45 kDa may have been produced by dimers and trimers (Monsalve et al. 1997).

Studies investigating gastrointestinal sensitization in children with atopic diathesis to proteins from turnip rape (Brassica rapa ssp. oleifera) analysed the levels of specific IgE against extracts from rapeseed oil (Poikonen et al. 2006). The results of the analysis showed that children known to have specific IgE against turnip rape protein have a strong cross-reactivity or co-reactivity to proteins from mustard and rapeseed seeds (Poikonen et al. 2009). Challenge tests with rapeseed oil or graded challenge tests with rapeseed proteins were not performed. An interesting finding from several of the studies was that sensitization to other allergens (birch pollen, peanut, soy or egg proteins) was found in a large number of children in the collectives (Kukkonen et al. 2014; Poikonen et al. 2008).

In a double-blind, placebo-controlled challenge test, none of the 14 children tested produced a marked positive reaction to turnip rape proteins in the prick test after ingesting 10, 100 and 1000 mg of purified turnip rape flour. Additionally, specific IgE against turnip rape oil was not found in any of the 14 test persons (no other details) (Kukkonen et al. 2014).

In the studies carried out with atopic children, specific IgE antibodies against the above-mentioned napin, an 2S albumin, from rapeseed and from turnip rape were found in the serum of the children (Puumalainen et al. 2006). The proteins napin and cruciferin (an 11S globulin) were later detected in an immunoblot analysis of the pooled serum from 5 children in cold-pressed, but not in refined rapeseed oil. The cold-pressed rapeseed oils were found to have a total protein content of about 0.012 to 0.046 mg/l (Puumalainen et al. 2015). According to other sources, unrefined or cold-pressed rapeseed oils contained up to 11 mg of protein per kg, while one refined rapeseed oil contained less than 0.2 mg/kg (see Table 1).

4.4.2.2 Soybean oil

Soybeans contain several allergenic proteins that are considered the cause of the allergic effects induced by soybean (products) (for an overview, see for example Cabanillas et al. 2018). Earlier findings relating to the sensitizing effects on the airways were described in great detail in the MAK documentation on soybean constituents (Greim 1997, available in German only). The observed responses to soy proteins can be divided into 3 groups. Sensitization to the allergens Gly m 1 (hydrophobic soy protein, a prolamin, 8.3 kDa) and Gly m 2 (a defensin, 8 kDa) is associated with airborne exposure to dusts containing proteins from soybean hulls. A second group comprises the responses after airborne or enteral exposure to the soybean protein Gly m 4 (17 kDa, homologue to Bet v 1), in most cases with co-sensitization to birch pollen (Bet v 1). Therefore, in cases with existing sensitization to Bet v 1, the responses may often be caused by cross-reactions to Gly m 4. An immunological gastrointestinal intolerance to foods containing soybean protein induced by the proteins Gly m 5 (β-conglycinin, a 7S globulin, 53–56 kDa) or Gly m 6 (glycinin, an 11S globulin, 52–61 kDa) occurs mainly in children. A food intolerance may be caused also by a number of other proteins. A trypsin inhibitor (Gly m TI, 20 kDa) is associated with baker's asthma.

To obtain the soybean oil, however, the protein fraction is almost completely separated during the extraction process and subsequent purification steps (including alkalization, bleaching). Purified or refined soybean oils generally contain protein in concentrations of less than 1 mg/kg oil (Cressey et al. 2011) or, according to other sources, between 100 and 270 µg/kg oil (EFSA 2007) (see Table 1). However, the values fall within a relatively large range depending on the origin of the raw materials, the processing and purification methods used and particularly also the methods of enrichment and determination applied for analysis. Cold-pressed oils contain proteins in concentrations of more than 1 mg/kg oil (see Table 1). Crude, non-degummed soybean oils may be composed of proteins in concentrations above 80 mg/kg oil (Rigby et al. 2011).

Tab. 1 Protein content in rapeseed and soybean oils

Oil	Enrichment / Analytical method	Protein content (mg/kg)	References
soybean oil			
1 refined and deodorized soybean oil	solvent fractionation / amino acid analysis after total hydrolysis	0.96	Tattrie and Yaguchi 1973
8 soybean oils (no other data)	ELISA (IgG of 2 children with sensitization to soya)	110–3300 (in 3 of 8 oils)	Porras et al. 1985
1 crude and 1 refined soybean oil	extraction with PBS / colorimetric (Bradford method)	1.9 (crude) 0.72 (refined)	Klurfeld and Kritchevsky 1987
5 soybean oils (no other data)	extraction with ammonium sulfate, solvent precipitation / colorimetric (Lowry method)	mean: 0.023 (0.014–0.04)	Awazuhara et al. 1998
2 refined and 3 crude soybean oils	acetone precipitation, extraction with PBS / colorimetric (Bradford method)	0.033–0.035 (refined) 0.090–0.138 (crude)	Paschke et al. 2001
1 deodorized and 1 cold-pressed soybean oil	extraction with PBS / not specified	0.32 (deodorized) 1.8 (crude)	Errahali et al. 2002 a
3 cold-pressed soybean oils	not specified	0.1–1.8 mg/l	Errahali et al. 2002 b
1 cold-pressed soybean oil	solvent extraction / precipitation (acetone:hexane, 1:1); dissolution in 6 N HCl / amino acid analysis after total hydrolysis	1.44	Martín-Hernández et al. 2008
2 refined soybean oils	extraction with PBS / colorimetric (Bradford method, BCA method) or amino acid analysis after total hydrolysis	0.16–0.19 (colorimetric) 0.96–1.66 (amino acid analysis)	Ramazzotti et al. 2008
29 soybean oils	extraction with borate / colorimetric (CBQCA method) extraction (C) and $NaHCO_3$ / amino acid analysis after total hydrolysis (A); for several other oils also: extraction with $NaHCO_3$ / colorimetric (BCA, Bradford or CBQCA method and amino acid analysis after total hydrolysis; Cressey et al. 2011)	8 × crude, degummed[a]: 0.3–16.2 (C) / 0.95–18.6 (A); 7 × neutralized: 0.06–1.7 (C) / 0.1–5.4 (A); 7 × neutralized and bleached: 0.03–0.32 (C) / 0.03–2.9 (A); 6 × neutralized, bleached and deodorized: 0.05–0.7 (C) / 0.03–0.43 (A); 1 × deodorized: 0.14 (C) / 0.057 (A)	Rigby et al. 2011
rapeseed oil			
1 cold-pressed, unrefined rapeseed oil; 1 refined rapeseed oil; 1 unrefined rapeseed oil	solvent extraction / precipitation (acetone:hexane, 1:1 (A) or acetone:methanol, 1:1 (B) or acetone with subsequent filtration (C)); dissolution in 6 N HCl / amino acid analysis after total hydrolysis	1 cold-pressed, unrefined rapeseed oil: 3.3 (A); 1.0 (B); 0.7 (C); 1 refined rapeseed oil: < 0.2 (A); 1 unrefined rapeseed oil: 11.1 (A)	Martín-Hernández et al. 2008

[a] in 3 crude, non-degummed oils: 86–88 mg/kg

BCA: bicinchoninic acid; CBQCA: (3-(4-carboxybenzoyl)quinoline-2-carboxaldehyde); ELISA: enzyme linked immunosorbent assay; PBS: phosphate-buffered saline solution

A publication described 4 cases in which patients reported experiencing "anaphylactic" reactions (no other details) at night after using new, viscoelastic pillows. According to the authors, a soybean oil that was not characterized in more detail was used in the production of the pillow stuffing. Additionally, all 4 patients reported having food-related rhinitis and asthma, although the sources were not clear. One female patient reported having a marked anaphylactic reaction after eating soy sauce. Prick tests with conventional allergens and foods, including soybean, and a corresponding IgE analysis yielded negative results in all patients. Other prick tests with extracts of soybeans and soybean hulls yielded negative results, while prick tests with extracts from the pillow stuffing yielded positive results (mean wheal diameter 8 × 8 mm ± 3 mm, mean wheal diameter for histamine 5 × 5 mm; no other details). Positive results were obtained for Gly m 5 in all patients by microarray-based IgE detection assay (immune solid-phase allergen chip). Bands that were compatible with the molecular masses of Gly m 5, Gly m 6 and the oleosins were detected by Western blot tests. In the dot blot assay, IgE binding to the aqueous fraction and to the lipoprotein fraction extracts of soybean and the core extract of the pillow was detected. Negative results were obtained in the serum of a control person for all

products tested (Armentia et al. 2013). However, no data were provided for other substances used in the manufacturing of the pillows. Furthermore, it is not certain that unmodified soybean oil was actually used to manufacture the pillows. It is likely that a chemically modified oil was used. Therefore, the plausibility of the findings is highly questionable and the causality of soybean oil cannot be evaluated.

4.4.2.2.1 Findings on the tolerability of soybean oil in persons with sensitization to soy protein

Three men and 4 women aged 18 to 63 years with an intolerance to soybean constituents were recruited for a double-blind, placebo-controlled crossover study of the (enteral) allergenicity of soybean oil. The time that had passed since the last exposure of the test persons that had led to an allergic reaction ranged from less than 1 year to 10 years. The oils used for testing were partially hydrogenated, non-hydrogenated and cold-pressed soybean oils; olive oil was used as the placebo control. The order of administration of the oils during the study was randomized. On the first day of testing, all test persons yielded positive results to soybean extract in the prick test, but none produced a positive response to any of the test oils. In the radioallergosorbent (RAST) assay, the binding percentage of serum-IgE antibodies to soybean allergens was 230% to 2800% in 6 test persons who were examined for this end point in comparison with the binding percentage found in the pooled serum from control persons. On the second day of the study, the test persons were successively administered the oils in gelatine capsules, receiving 2, 5 and 8 ml of one of the oils. Each exposure was followed by a 30-minute observation period. The other oils were administered at intervals of at least 6 days. None of the test persons developed immediate or delayed adverse reactions (Bush et al. 1985).

A review published by this research group described later, double-blind, placebo-controlled (canola oil) studies in which 28 volunteers with sensitization to the constituents of soybeans (anamnesis, positive results in the prick test, positive results in the RAST) did not show reactions after they had ingested 1, 5 and 10 g of 4 refined soybean oils (with a relatively high protein content; no other details) (Taylor et al. 2004).

In a challenge study initiated by the European Food Safety Authority (EFSA), 27 test persons between the ages of 12 and 62 years were administered 12, 24 and finally 48 ml of a mixture of soybean oil with a protein content of 0.15 mg/kg at intervals of 30 minutes. Rapeseed oil was used as the control. Two test persons reported having symptoms on the oral mucosa after ingesting soybean oil and rapeseed oil. Three test persons reported the same type of symptoms after ingesting soybean oil and three after ingesting rapeseed oil. Without providing any further information, the authors determined that the minimum dose of soy protein required to elicit gastrointestinal intolerance symptoms was in the range of 1.5 and about 11.5 µg. In total, about 12 µg of protein was ingested with the soybean oil (Cressey et al. 2011).

In the serum of 4 children aged 1 to 8 years with (gastrointestinal) sensitization to soybean constituents (positive results in the prick test), IgE or IgG4 did not bind to extracts of protein from soybean oil. In 1 of the 4 test persons, a challenge test with soya yielded positive results. The patient's clinical history revealed that the symptoms were exacerbated by soybean oil. In addition, IgE binding to soy lecithin proteins was detected in the serum of this test person (bands around 30 kDa) (Awazuhara et al. 1998).

In a Western blot analysis using the serum of a woman sensitized to soybean constituents (RAST 18.9 kU/l), the proteins extracted from 2 soybean oils by PBS (1.89 mg/kg from a cold-pressed oil and 0.32 mg/kg from a deodorized oil) produced a distinct band at 56 kDa (in addition to a very weak band at 28 kDa) (Errahali et al. 2002 a). In other studies, immunoblotting with the pooled serum of 3 persons sensitized to soy protein produced bands at 28.2, 32.8, 43, 44, 56.6 and 58 kDa. Without providing any further information, the authors reported that an oral challenge assay with crude soybean oil yielded positive results in a patient who had previously had multiple anaphylactic reactions after ingesting soy products (Zitouni et al. 2001). The protein that produced a band at 56 kDa was later identified as (soybean) β-amylase (Errahali et al. 2004).

In a gel electrophoresis experiment, protein fractions extracted from 2 refined soybean oils by acetone precipitation produced patterns similar to those of fractions obtained from 3 unrefined soybean oils. However, unlike the latter, they did not exhibit IgE binding activity in the immunoblot assay (9 pooled sera, enzyme allergo-sorbent test (EAST) classes 1–4). In the EAST assay, these 2 fractions did not exhibit inhibitory activities against soy protein extracted from soybeans; the other 3 fractions led to about 25% to at most 53% inhibition (Paschke et al. 2001).

The findings of several double-blind oral challenge studies carried out in test persons with soybean flour revealed that the small amounts of protein that refined soybean oils contain are quite unlikely to induce allergic reactions, at least after oral administration:

In a tricentric study (Zurich, Milan, Odense) that investigated 30 test persons sensitized to soy protein (positive results in a challenge test or clinical history with reliable data; ages: 1 to 69 years, average age: 26.4 years), 23 of the test persons underwent a double-blind, placebo-controlled challenge test with 9 increasing doses of soy flour (2 mg to 31.8 g soy flour; maximum cumulative dose: 50 g soy flour, equivalent to a soy protein dose from 1 mg to a maximum cumulative dose of 26.5 g). The doses were administered at intervals of 15 minutes until objective symptoms developed or the maximum amount was reached. In 4, 2 and another 4 test persons, subjective symptoms developed only after administration of a total dose of 5.3 mg, about 84 mg or about 240 mg of soy protein, respectively. Objective symptoms were observed in 2 of these 10 test persons at doses of about 240 mg and above (urticaria or blisters of the oral mucosa). The doses at which subjective or objective symptoms first became noticeable did not correlate with the prick test results (prick-to-prick test with soy protein and prick test with soy extract) or with the levels of specific IgE antibodies against soy protein (CAP system; 4 × negative (< 0.35 kU/l), 3 × slightly increased (0.41 to 0.54 kU/l), 3 × increased (1.54 to 3.05 kU/l)). By contrast, the levels of specific IgE antibodies against both Gly m 4 (1.10 to 9.34 kU/l) and Bet v 1 (4.65 to > 100 kU/l) were increased in 8 test persons (Ballmer-Weber et al. 2007).

Another study of soybean foods, including a mixture of 2 soybean oils, and their ability to induce allergic responses was carried out with 8 children; however, the study design raises ethical concerns. The 8 children were sensitized passively by injecting the serum of a female patient who had produced an allergic response to soybeans, among other allergens. The presence of antibodies against soybean constituents was first confirmed in her serum by passive sensitization of 8 adult volunteers and the challenge by injection of 20 µl of a soybean extract (1:1000). One to 3 days later, the children drank 42 to 56 g of a mixture containing soybean oil. In 4 children in each case, no reactions were observed at the injection site after 1.5 and 24 hours, respectively; however, ingestion of soybean flour at a later time point induced reactions at the injection site after about 1 to 2 hours (Ratner et al. 1955).

Study reports describing possible allergic reactions after enteral administration of soybean oil (proteins) via pharmaceutical preparations (Dueñas-Laita et al. 2009; Pineda et al. 2011) or via dietary supplements (Moneret-Vautrin et al. 2002) have not been included in the evaluation because of the unclear identity of the soybean oils (or soybean formulations) used. This applies also to reports about possible allergic reactions after intravenous injection of pharmaceuticals containing soybean oil (Richard et al. 2016).

4.4.3 Summary

After oral administration of refined/purified soybean oils, no evidence was found that these oils induce sensitizing effects on the gastrointestinal tract. Corresponding studies have not been carried out with rapeseed oils. As the use of different methods of processing and detection introduces a relatively large degree of uncertainty with regard to the quantification of the protein fractions in rapeseed and soybean oils, it is assumed that exposure to proteins in an amount sufficient to induce or trigger an allergic reaction on the skin or the airways is not to be expected under workplace conditions. However, this does not apply to crude, unrefined rapeseed or soybean oils. As these may contain markedly higher concentrations of proteins, it may be necessary to examine their protein fractions separately.

4.5 Reproductive and developmental toxicity

There are no data available.

4.6 Genotoxicity

There are no data available.

4.7 Carcinogenicity

As previously described in the documentation for oleic acid, numerous epidemiological studies have investigated a possible association between an increased uptake of fat or fatty acids with the diet and the development of tumours. As there is controversy relating to the mechanisms involved and these are not relevant to the exposure situation found at the workplace (Greim 2002), these studies have not been included in the evaluation of carcinogenicity at the workplace.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

The LC_{50} value for inhalation exposure of rats to **rapeseed oil** was above 3260 mg/m³, the highest attainable concentration (no other details; EFSA 2013).

5.1.2 Oral administration

The LD_{50} value for oral exposure of rats to **rapeseed oil** was above 2000 mg/kg body weight (no other details; EFSA 2013).

The acute oral toxicity of undiluted **palm oil** was studied in 5 rats (strain and sex not specified). One animal died 1 day after administration, another after 6 days. The LD_{50} value was above 5000 mg/kg body weight (Johnson 2000).

5.1.3 Dermal application

The LD_{50} value for dermal exposure of rats to **rapeseed oil** was above 2000 mg/kg body weight (no other details; EFSA 2013).

5.1.4 Intravenous and intratracheal injection

The LD_{50} value for intravenous injection of **soybean oil** in rats was 68 ml/kg body weight (NCBI 2021 c).

In rabbits, mineral oil followed by animal oils (milk fat, rabbit fat, cod liver oil, **lard oil**) and vegetable oils (poppyseed oil and sesame oil) proved to be the most toxic after single intratracheal administration (Pinkerton 1928).

Animal studies with intratracheal injection of vegetable oils (in so far as these did not contain irritants, as naturally occur in chaulmoogra oil or croton oil) did not find evidence of specific pathological effects (no other details; Shoshkes et al. 1950).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

There are no data available.

One study, however, is available that investigated corn oil and arachis oil. In this study, female and male Carworth Farms albino mice (groups of 5 to 7 animals) were exposed for up to 30 days (5 to 8 hours/day, 5 days/week) to oil mists from 2 different vegetable oils (corn oil, arachis oil, mean mass median diameter 2.5 µm). The oil mists were generated by nebuliser. A dye (Blue ZA) was used to determine the concentration. The concentrations were 12 600 and 10 600 mg/m³, respectively. Of the 2 groups exposed to corn oil, 5 of 6 and 6 of 7 animals, respectively, survived and of the 2 groups exposed to arachis oil, 4 of 5 and 6 of 6 animals, respectively, survived. The animals were examined

immediately after the last exposure. The oils were found to be retained in the lungs and a local foreign-body reaction had developed in the lung parenchyma. The histological findings corresponded to those of acute lipoid pneumonia (see Section 2; Shoshkes et al. 1950).

5.2.2 Oral administration

Table 2 gives an overview of the studies that investigated repeated oral exposure to rapeseed oil, palm oil, soybean oil and lard. As there were no studies with lard oil available, studies that examined lard were used for the evaluation instead. Extensive toxicological studies, particularly of dose dependency, were not available.

After rats were given low erucic acid (< 2%) **rapeseed oil** with the feed in doses of up to 9000 mg/kg body weight and day for a period of up to 10 weeks, no adverse effects were found with the exception of increased aldosterone levels in the plasma. However, this effect is of unclear toxicological significance (Mohamed et al. 1987; Ohara et al. 2008). The rapeseed oil dose of 9000 mg/kg body weight and day was established as the NOAEL (no observed adverse effect level). In rats given low erucic acid rapeseed oil with the feed for several weeks, vacuolization of the hepatocytes, lipid accumulation and focal necrosis in the liver were observed at doses of about 9000 mg/kg body weight and day and above (Badawy et al. 1994; Kramer et al. 1979).

Several studies in rats given **palm oil** with the feed at doses up to 13 500 mg/kg body weight and day for up to 3 months did not detect any effects on growth, serum enzymes, haematology, blood biochemistry or urine parameters; histopathological examination of various organs did not yield unusual findings (Johnson 2000). The initial effects observed in this species were an increase in the enzyme activities of alkaline phosphatase and aspartate aminotransferase (Owu et al. 1998). The free cholesterol and triglyceride levels were increased in the plasma at 21 000 mg/kg body weight and day (Purushothama et al. 1994). Palm oil given to rabbits with the feed at a dose of about 6000 mg/kg body weight and day led to increased cholesterol and triglyceride levels in the plasma and increased blood pressure after 8 weeks (Kennedy et al. 1978). In a study that was not reported in detail, rats were given 10% or 30% palm oil with the feed for 4 to 14 weeks (palm oil doses of about 9000 or 27 000 mg/kg body weight and day based on a conversion factor of 0.09 as recommended by EFSA (2012) for subchronic studies). Decreased body weight gain and a reduction in the size of liver cells, a loss of cellular radial architecture and a higher ratio of alanine aminotransferase to aspartate aminotransferase in the blood were observed at the high dose (Edem 2002).

Studies were carried out to assess the toxicity of stearidonic acid **soybean oil** because the intake of stearidonic acid is increased when stearidonic acid soybean oil is added to human foods. Stearidonic acid soybean oil is made from soybean plants that have been genetically modified by introducing genes for Δ6 and Δ15 desaturases. These enzymes convert linoleic and alpha-linolenic acid to stearidonic acid. This study used soybean oil as the control. In a 28-day pilot study carried out in compliance with OECD Test Guideline 407 with administration of gavage doses to Sprague Dawley-Crl:CD(SD) rats, no adverse effects were observed after treatment with soybean oil doses of up to 3000 mg/kg body weight and day. The NOAEL for systemic toxicity induced by soybean oil was 3000 mg/kg body weight and day, the highest dose tested. The pilot study was followed by a 90-day/one generation study that used oil from near-isogenic lines of soybean as the control. This oil was extracted from soybeans of the same plant line as stearidonic acid soybeans. However, unlike stearidonic acid soybeans, these soybean plants were not first modified to include genes for Δ6 and Δ15 desaturases. In this study, animals treated with menhaden oil (fish oil) at a dose of 4000 mg/kg body weight and day and animals treated with stearidonic acid soybean oil at 4000 mg/kg body weight and day had lower cholesterol and triglyceride levels than animals treated with near-isogenic soybean oil at 4000 mg/kg body weight and day (Hammond et al. 2008; see Section 5.5.1). The publication did not include historical control values for these 2 parameters. In male Sprague Dawley rats, soybean oil given with the feed for 24 weeks at a dose of about 13 500 mg/kg body weight and day did not lead to effects on body weight gains, feed consumption or blood pressure. There was no evidence of oxidative stress or endothelial dysfunction (Leong et al. 2010).

Lard ingested by rats for a period of 5 weeks at a dose of about 13 500 mg/kg body weight and day did not lead to noticeable effects on the liver of the animals (Lee et al. 2016). In the same species, obesity and an increase in fasting insulin levels were observed after 12 weeks at a dose of about 30 600 mg/kg body weight and day (CIREP 2001). In

mice, increased triglyceride levels in the liver, including steatosis, were observed after ingestion of lard via the diet for 4 weeks at a dose of about 108 00 mg/kg body weight and day (Lee et al. 2017) and increased body weight gains and a shortened lifespan were observed after oral doses were given for several months (CIREP 2001). NOAELs could not be derived from these studies.

Therefore, effects become noticeable only in the gram/kg body weight range. Due to the structure of the triglycerides, rapeseed, palm and soybean oils as well as lard and lard oil are unlikely to cause severe systemic toxicity.

Tab. 2 Effects of rapeseed, palm and soybean oil and lard after repeated oral exposure

Species, strain, number per group	Exposure	Findings	References
rapeseed oil			
rat, Sprague Dawley, 10 ♂	**10 days,** rapeseed oil (1%–49.2% erucic acid), 20% by weight in the feed; about 24 000 mg/kg body weight and day[a)]; compared with groups given rapeseed oil and margarine, arachis oil	**about 24 000 mg/kg body weight**: up to 1% erucic acid in the feed: no effects on the myocardium; 2% erucic acid in the feed and above: effects on the myocardium: lipoidosis with a dose-dependent increase in severity	Engfeldt and Brunius 1975 a
rat, Sprague Dawley, 5–7 ♂	**10 or 80 days,** rapeseed oil (40.1% or 49.2% erucic acid), 10% (80 days) or 20% (10 days) by weight in the feed; about 9000[b), c)] or 24 000[a), c)] mg/kg body weight and day; compared with groups given arachis oil (0.1% erucic acid)	**about 9000 and 24 000 mg/kg body weight**: no differences found in germ-free and non-germ-free rats with respect to the development of myocardial effects (histiocytic infiltration)	Engfeldt and Gustafsson 1975
rat, strain and number not specified, age: weaned, about 21 days	**up to 28 days,** partially hydrogenated rapeseed oil (considerable erucic acid content, no other data), 20% by weight in the feed; about 24 000 mg/kg body weight and day[a)]; compared with groups given different oils	**about 24 000 mg/kg body weight**: myocardial degeneration after 3–5 days	Heggtveit et al. 1973
rat, Sprague Dawley, 8 animals, sex not specified	**6 weeks,** rapeseed oil (high and low erucic acid content, no other data), 10% by weight in the feed; about 9000 mg/kg body weight and day[b)]; hydrogenated or partially hydrogenated rapeseed oil; compared with a group given corn oil	**about 9000 mg/kg body weight**: low erucic acid content: serum: triglycerides ↑ (without statistical significance); liver: vacuolization of hepatocytes; kidneys: slight degenerative changes; high erucic acid content: body weight gains ↓; no unusual findings: total lipids, total cholesterol, AST, ALT	Badawy et al. 1994
rat, strain and number not specified, age: weaned, about 21 days	**45 days,** rapeseed oil (erucic acid content not specified), 5% by weight in the feed; about 4500 mg/kg body weight and day[b)]; compared with a group given cottonseed oil; another group was treated with rapeseed and cottonseed oil (1:1), 5% by weight, for comparison	**about 4500 mg/kg body weight**: no unusual findings: serum: albumin, total protein, total bilirubin, AST, ALT, alkaline phosphatase, cholesterol, triglycerides, total lipids, urea	Mohamed et al. 1987

Tab. 2 *(continued)*

Species, strain, number per group	Exposure	Findings	References
rat, Wistar, 8 ♂	**10 weeks**, rapeseed oil (0.7% erucic acid), 10% by weight in the feed; about 9000 mg/kg body weight and day[b)]; compared with a group given soybean oil	**about 9000 mg/kg body weight**: plasma: aldosterone ↑ (1280 ± 250 pg/ml; soybean oil group: 897 ± 24 pg/ml, significance unclear as no changes in kidneys); no unusual findings: body weight gains, feed consumption, haematology (no data), blood biochemistry (total cholesterol, free cholesterol, triglycerides, phospholipids, non-esterified fatty acids, glucose, alkaline phosphatase, urea, creatinine, K^+, Cl^-, Na^+), urinalysis (volume, Na^+, K^+, Cl^-, creatinine), histopathology (brain, heart, lungs, liver, spleen, kidneys, adrenal glands, testes, epididymis, prostate gland)	Ohara et al. 2008
rat, Sprague Dawley and Chester Beatty, 50 ♂, age: 3 weeks	**16 weeks**, rapeseed oil (0.8% or 25.5% erucic acid), 20% by weight in the feed; about 18 000 mg/kg body weight and day[b)]; compared with a group given corn oil	**about 18 000 mg/kg body weight**: rapeseed oil containing 0.8% erucic acid: liver: lipid accumulation (to the same extent in both strains), focal necrosis (Sprague Dawley more susceptible than Chester Beatty), bile duct hyperplasia (mainly in Chester Beatty), a few animals: pericholangitis; rapeseed oil containing 25.5% erucic acid: growth ↓; heart: lipid accumulation and focal necrosis, organ weights ↑; liver: lipid accumulation (to the same extent in both strains), focal necrosis (Sprague Dawley more susceptible than Chester Beatty), a few animals: pericholangitis	Kramer et al. 1979
rat, Sprague Dawley, 20 ♂, 20 ♀	**160 days (22.9 weeks)**, rapeseed oil (46.6%–49.2% erucic acid), 20% by weight in the feed; about 18 000 mg/kg body weight and day[b), c)]; compared with groups given rapeseed oil and arachis oil containing various amounts of erucic acid	**about 18 000 mg/kg body weight**: heart: myocardial fat accumulation, time-dependent decrease in the number of fat droplets, histiocytic infiltration after 40 days, macrophages, myolysis, proliferation of fibroblasts and ultimately scar formation	Engfeldt and Brunius 1975 b
rat, strain not specified, 10 ♂, 10 ♀, age: 28 days	**up to 25 weeks**, rapeseed oil (0.2% erucic acid), 20% by weight in the feed; about 18 000 mg/kg body weight and day[b), c)]; compared with a group given arachis oil	**about 18 000 mg/kg body weight**: ♀: urine: osmolarity ↓; no unusual findings: electrocardiogram	Berglund 1975
rat, strain not specified, 10 ♂, 10 ♀, age: 28 days	**up to 25 weeks**, rapeseed oil (0.2% erucic acid), 20% by weight in the feed; about 18 000 mg/kg body weight and day[b), c)]; compared with a group given arachis oil	**about 18 000 mg/kg body weight**: ♀: urine: osmolarity ↓; no unusual findings: electrocardiogram	Berglund 1975
rat, Sprague Dawley, 5–6 ♂	**24–26 weeks**, rapeseed oil (8.9% erucic acid), 10% by weight in the feed; about 9000 mg/kg body weight and day[b), c)]; compared with groups given sunflower oil, 8.9% erucic acid in the feed (without rapeseed oil)	**about 9000 mg/kg body weight**: feed consumption ↓ (first 4 weeks), vasoconstrictor response to norepinephrine ↓ (also in the erucic acid group), contractile reserve capacity ↓ (not in the erucic acid group); no unusual findings: electrocardiogram	de Wildt and Speijers 1984
rat, Wistar, 64 animals, sex not specified, weaned	**28 weeks**, rapeseed oil (1.1% erucic acid), equivalent to 15% by weight in the feed; about 13 500 mg/kg body weight and day[b)]; no group used as a comparison	**about 13 500 mg/kg body weight**: heart: succinate dehydrogenase activity correlated with histologic damage	Grynberg et al. 1984

Tab. 2 *(continued)*

Species, strain, number per group	Exposure	Findings	References
rat, Wistar, 75 ♂, weaned	**107–110 weeks**, including mating, control group: refined rapeseed oil (1% cetoleic acid, 22:1, (11*Z*)-11-docosenoic acid), equivalent to 16% by weight in the feed; total fat content 20% by weight in the feed (additionally soybean and linseed oil); weeks 1–5: 11 000 mg rapeseed oil/kg body weight and day, weeks 88–90: 3400 mg rapeseed oil/kg body weight and day, mean: 4100 mg/kg body weight and day (no data for the other time periods); compared with groups given partially hydrogenated fish oil (with low and high cetoleic acid contents) and soybean oil; interim examination: 10 ♂ after 4 days and 15 ♂ after 26 weeks	**4100 mg/kg body weight**: in comparison with fish oil and soybean oil: survival after 107–110 weeks: 26/50 (52%); body weights and feed consumption slightly ↓; heart: mild lipidosis; in comparison with soybean oil: blood: triglycerides ↓ (weeks 26 and 52, reversible); liver: centrilobular fatty vacuolization ↑; forestomach: polymorphonuclear leukocyte infiltration; eyes: retinal degeneration; no unusual findings: blood chemistry and urinalysis, ophthalmoscopy, organ weights (adrenal glands, brain, gastrointestinal tract, ovaries, testes, heart, kidneys, liver, lungs, lymph nodes, pituitary gland, prostate gland, spleen, thymus gland, thyroid gland, uterus), histopathological examination of about 23 organs in total (exceptions see above); no association between cardiac lipidosis and cetoleic acid levels; diffuse myocardial fibrosis correlated with age in all groups	Duthie et al. 1988 (see Section 5.5 and Section 5.7)
palm oil			
rat, Wistar, 5 ♂, 5 ♀, weaned	**28 days**, palm oil, 10% by weight in the feed; about 12 000 mg/kg body weight and day[a]; 10% casein protein in the feed; compared with groups given protein-free feed, 10% refined arachis oil and 10% casein protein, 10% refined palm olein oil and 10% casein protein	**about 12 000 mg/kg body weight**: no unusual findings: growth, fat uptake, serum enzymes, haematology	Johnson 2000
rat, Wistar, 10 ♂	**6 weeks**, palm oil, 20% by weight in the feed; about 21 000 mg/kg body weight and day (amount of feed consumed: 11.6 g/rat and day, mean body weights using starting and final weights 111 g); compared with groups given 20% safflower oil in the feed	**21 000 mg/kg body weight**: plasma: free cholesterol ↑, LDL-C and VLDL-C ↑, HDL-C ↓, phospholipids ↑, triglycerides ↑; no unusual findings: organ weights kidneys, spleen, heart	Purushothama et al. 1994
rat, Wistar, 15 ♂, 15 ♀, weaned	**90 days**, palm oil, 10% by weight in the feed; about 9000 mg/kg body weight and day[b]; compared with groups given 10% refined arachis oil, 10% refined palm oil in the feed	**about 9000 mg/kg body weight**: no unusual findings: growth, fat uptake, serum enzymes, haematology	Johnson 2000
rat, Sprague Dawley, 10 ♂, 10 ♀, age: 6 weeks	**3 months**, palm oil, 15% by weight in the feed; about 13 500 mg/kg body weight and day[b]; 20% casein protein in the feed; compared with groups given 15% heated palm oil and 20% casein protein	**about 13 500 mg/kg body weight**: no unusual findings: haematology, blood biochemistry, urine parameters, histopathological examination (brain, thyroid gland, heart, liver, spleen, kidneys, gonads, adrenal glands), growth	NCBI 2021 b
rat, Wistar, 7 ♂	**18 weeks**, crude palm oil, 15% by weight in the feed; about 13 500 mg/kg body weight and day[b]; compared with a group given feed without palm oil	**about 13 500 mg/kg body weight**: crude oil: alkaline phosphatase and AST ↑, but not ALT	Owu et al. 1998
rabbit, New Zealand, 5 animals, sex not specified	**up to 8 weeks**, palm oil, 20% by weight in the feed; about 6000 mg/kg body weight and day[d]; compared with groups given feed containing 200 g safflower oil or feed containing 200 g each of palm oil and cellulose	**about 6000 mg/kg body weight**: plasma: cholesterol ↑, triglycerides ↑, blood pressure ↑ in comparison with pre-treatment levels	Kennedy et al. 1978

Tab. 2 *(continued)*

Species, strain, number per group	Exposure	Findings	References
soybean oil			
rat, Sprague Dawley Crl:CD(SD), 10 ♂, 10 ♀	**28 days**, pilot study, experimental design adapted from OECD Test Guideline 407, Group 1: feed control group, no oil, Group 2: 3000 mg soybean oil/kg body weight and day, Group 3: 300 mg SDA soybean oil/kg body weight and day and 2700 mg soybean oil/kg body weight and day, Group 4: 1000 mg SDA soybean oil/kg body weight and day and 2000 mg soybean oil/kg body weight and day, Group 5: 3000 mg SDA soybean oil/kg body weight and day, gavage, 7 days/week	**3000 mg soybean oil/kg body weight**: NOAEL for systemic toxicity; no unusual findings: survival, body weights, feed consumption, clinical symptoms, haematology, serum chemistry, urinalysis, organ weights, histological examination of about 40 organs	Hammond et al. 2008
rat, Sprague Dawley Crl:CD(SD), 25 ♂, 45 ♀ (25 ♀: mated)	**90-day/one generation study**, experimental design adapted from OECD Test Guidelines 408 and 415, 90 days ♂/♀: treatment 70 days before mating and during mating, F0 ♀: treatment 70 days before mating, during mating and up to weaning on PND 21, F1: treatment up to PND 21, Group 1 (control group): 4000 mg near-isogenic soybean oil[e)]/kg body weight and day, Group 2: 4000 mg menhaden oil (fish oil)/kg body weight and day, Group 3: 1500 mg SDA soybean oil/kg body weight and day and 2500 mg near-isogenic soybean oil/kg body weight and day, Group 4: 4000 mg SDA soybean oil/kg body weight and day, feed	**4000 mg soybean oil/kg body weight (in comparison with menhaden oil or SDA soybean oil)**: ♂/♀: cholesterol ↑ and/or triglycerides ↑, no data for cholesterol and triglyceride levels of the historical controls; no unusual findings: survival, body weights, feed consumption, organ weights, gross-pathological and histopathological examinations	Hammond et al. 2008; see Section 5.5.1
rat, Sprague Dawley, 7 ♂	**24 weeks**, soybean oil, 15% by weight in the feed, 0, about 13 500 mg/kg body weight and day[b)], compared with a group given feed without added oil	**about 13 500 mg/kg body weight**: no unusual findings: body weight gains, feed consumption, blood pressure, oxidative stress, endothelial dysfunction; animal model for the investigation of biochemical and vascular mechanisms that contribute to an increase in blood pressure	Leong et al. 2010
lard			
rat, Wistar, no other data	**6 weeks**, about 4500–33 300 mg/kg body weight and day[b), c)], compared with a group given summer butterfat (no other details)	**about 4500–33 300 mg/kg body weight**: no unusual findings: food efficiency, mortality	CIREP 2001

Tab. 2 *(continued)*

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, ♂, number not specified	**12 or 50 weeks**, about 30 600 mg/kg body weight and day[b), c)], compared with groups given corn oil, control group (no other details)	**about 30 600 mg/kg body weight**: serum: fasting insulin concentration ↑, obesity	CIREP 2001
mouse, C57BL/6N, 4 ♂	**1, 2 or 4 weeks**, lard, 54% by weight in the feed; about 108 000 mg/kg body weight and day[a)], examination of the animals at the age of 12 weeks = end of study, compared with groups given untreated feed	**about 108 000 mg/kg body weight**: liver: after 4 weeks: triglycerides ↑, steatosis	Lee et al. 2017
mouse, C57BL, no other data	**Group 1: 5 months beginning at age 1, 7 or 12 months, Group 2: beginning at age 6 or 12 months until end of life,** lard, 25% by weight in the feed; about 50 000 mg/kg body weight and day[b)], compared with groups given lard-free feed	**about 50 000 mg/kg body weight**: body weight gains ↑, lifespan ↓	CIREP 2001
mini pigs, no other data	**12 or 50 weeks**, lard, 9% by weight in the feed; about 3057 mg/kg body weight and day[f)], compared with groups given sunflower oil and olive oil, 9% by weight in the feed	**about 3057 mg/kg body weight:** serum: total cholesterol ↑ (12 weeks, not 50 weeks), LDL ↑, HDL ↓	CIREP 2001

a) conversion factor 0.12 for rats and 0.2 for mice for subacute studies (EFSA 2012)
b) conversion factor 0.09 for rats and 0.2 for mice for subchronic studies (EFSA 2012)
c) caloric intake equivalent to about double the fat intake by weight
d) assuming a body weight of 2 kg and daily feed intake of 60 g (Nielsen et al. 2008, p. 338)
e) from soybeans of the same plant line as SDA soybeans, but without the genes for Δ6 and Δ15 desaturases that SDA soybeans contain
f) assuming a body weight of 16.9 kg and daily feed intake of 574 g (Bollen et al. 2005)
ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDL/HDL: low/high density lipoprotein; LDL-C: low density lipoprotein cholesterol; PND: postnatal day; SDA: stearidonic acid (20%); SDH: succinate dehydrogenase; VLDL-C: very low density lipoprotein cholesterol

This evaluation does not include studies with stroke-prone spontaneously hypertensive rats (Huang et al. 1996; Naito et al. 2000, 2003) because these animals have been bred for use as a model for high blood pressure and stroke.

5.2.3 Dermal application

There are no data available.

5.2.4 Intravenous injection

There are several studies that used an intravenous route of administration to investigate parenteral nutrition with **soybean oil** in rats and other species (NCBI 2021 c). Oleic acid is known to cause effects in the lungs (haemorrhagic alveolitis, pulmonary oedema, adverse effects on breathing, hypoxaemia and pulmonary fibrosis) in a number of species after only a single intravenously administered dose. The mechanism involved is not known (Greim 2002). Studies in guinea pigs found that the partial oxygen pressure of the arterial blood was decreased to a lesser extent after administration of soybean oil than after administration of oleic acid (Ishitsuka et al. 2009). BALB/c mice (lipid emulsion: 44 male animals in total, 20 male control animals) served as the animal model for endotoxin-induced acute lung injury. For 3 days, the animals were intravenously administered a **soybean oil**-based lipid emulsion (1500 mg lipids/kg body weight and day) via an osmotic mini pump. A single dose of 10 µg endotoxin (lipopolysaccharides) in saline solution was then instilled intratracheally in each mouse. The animals of the comparison group were administered saline solution. The animals were examined after 0, 4 and 24 hours. In the treated animals, a time-dependent

decline in the number of splenic and circulating lymphocytes was observed in addition to an increase in apoptosis. Also mortality was increased (Bi et al. 2010). The toxicity of a **soybean oil fat emulsion** used for parenteral nutrition (15% soybean oil neutral fats, 1.2% non-hydrogenated soy phosphatides, 5% glycerol) was studied in groups of 10 beagle dogs (male and female animals, no other details) by administering doses of 0, 4000 or 9000 mg/kg body weight and day intravenously to the animals for 28 days. The control group was given a dextrose Ringer's solution. Reduced feed consumption, inactivity, lethargy and decreased haemoglobin and haematocrit values were observed at 9000 mg/kg body weight and day. These kinds of effects were not noticeable at 4000 mg/kg body weight and day. Mortality and a loss of body weight did not occur. In individual cases, lethargy, vomiting, diarrhoea, loss of appetite and fever were observed; these effects were not dependent on the dose (Reimold 1979).

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

Rapeseed oil is described as not irritating to the skin (no other details; EFSA 2013).

The skin irritation potential of undiluted **palm oil** was investigated in 9 rabbits (strain and sex not specified) in a single-insult occlusive patch test. Two hours after application, 5 rabbits were found to have an irritation score of 0 and the remaining 4 had a score of 0.5. At the reading 24 hours after application, 1 rabbit still had an irritation score of 0.5, while the irritation score of the remaining animals was 0. The primary irritation index was 0.22 (on a scale with a maximum score of 8) and the test substance was evaluated as not irritating. A second study (same procedure) investigated another group of 9 rabbits. Two hours after application, 6 animals had an irritation score of 1. After 24 hours, 4 of these animals still had a score of 1. The primary irritation index was 0.67 and the test substance was evaluated as causing minimal irritation (no other details; Johnson 2000). Undiluted palm oil caused almost no to minimal irritation on the rabbit skin (no other details; Burnett et al. 2017).

No evidence of irritation induced by **soybean oil** was found on the skin of pigs and nude mice (no other details; NCBI 2021 c).

5.3.2 Eyes

Rapeseed oil does not cause irritation of the eyes (no other details; EFSA 2013).

The eye irritation potential of undiluted **palm oil** was investigated in 6 rabbits (strain and sex not specified). The eyes were not rinsed after instillation of the test substance. The Draize scale was used to assess the reactions (scale: 0 to 110). On day 1 following instillation, the 6 rabbits had an overall eye irritation score of 3. On day 2 following instillation, they had an overall score of 1. No reactions were observed on the third day after instillation. The substance was classified as causing minimal eye irritation (no other details; Johnson 2000). Undiluted palm oil caused minimal irritation in the eyes of rabbits (no other details; Burnett et al. 2017).

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

A study investigated a pesticide that was formulated with 90% **rapeseed oil** and 2% pyrethrum; the remaining ingredients were not reported. A maximization test was carried out in female albino Dunkin Hartley guinea pigs in compliance with OECD Test Guideline 406. The intradermal induction was carried out with 20% test substance in water followed by topical application of the undiluted test substance on skin pre-treated with sodium lauryl sulfate (10%). A reaction was not observed on the skin of any of the animals 24 or 48 hours after the challenge with undiluted test substance (European Commission 2008).

The sensitization potential of **palm oil** was tested in 4 groups of 10 female Hartley guinea pigs using the maximization test according to Magnusson and Kligman. A formulation of 5% palm oil in propylene glycol was used for intradermal induction followed by occlusive application of undiluted palm oil for 48 hours for topical induction. The 24-hour occlusive challenge treatment was carried out with 5% palm oil in petrolatum. None of the 10 test animals had reacted after 24 and 48 hours (Johnson 2000). However, as the study did not include pre-treatment with sodium lauryl sulfate and the challenge was carried out with only a 5% solution, the reliability of the test results is uncertain.

The REACH registration dossier for soybean oil, deodorizer distillate (CAS number 68783-88-0), includes a maximization test with **soybean oil** that obtained negative results in a group of 10 guinea pigs. The intradermal and topical induction was performed with 5% soybean oil and undiluted soybean oil, respectively, and the challenge treatment was carried out with 50% soybean oil. None of the 10 animals produced a reaction. The report did not include a characterization of the oil, data for the vehicle or for the use of positive and negative controls (ECHA 2013).

There are no studies available for **lard oil**.

5.4.2 Sensitizing effects on the airways

There are no data available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

In a study of carcinogenicity and chronic toxicity, male Wistar rats were given refined **rapeseed oil** (containing 1% 22:1 fatty acids) with the feed for 107 to 110 weeks. From weeks 1 to 5, they received doses of 11400 mg/kg body weight and day and from weeks 88 to 90, doses of 3400 mg/kg body weight and day (mean: 4100 mg/kg body weight and day, no data for the other time periods). One of the objectives of the study was to assess reproductive toxicity. The animals were given feed containing rapeseed oil for 10 weeks (males) or 4 weeks (females) before mating, during the 1-week mating period and up to the end of the experiment. In each case, 1 male was mated with 1 female animal. In all treatment groups, the parameters fertility, number of living offspring per litter and viability of the offspring were in the normal range. No unusual findings were determined by histological examination in the reproductive organs of the male animals. The females were not examined (see Section 5.2.2; Duthie et al. 1988).

In a 4-generation study, Wistar rats were given **palm oil** that had been refined using a standard process and palm oils that had been heated using 4 different processes. No unusual findings with respect to fertility and general toxicity were observed in the group given the palm oil that had been treated using a standard refining process (Johnson 2000). Two other studies of reproductive toxicity in Sprague Dawley and Wistar rats given 15% and 10% palm oil with the feed did not report unusual findings relating to fertility and in utero growth (Johnson 2000). In female Sprague Dawley [CrI:CD(SD)BR] rats (15 to 16 animals per group), 20% palm oil in the feed did not have any effect on sexual maturation and endocrine function. Rats that were given 5% or 20% corn oil in the feed served as a comparison (Johnson 2000).

In a 90-day/one-generation study, no effects on fertility and the reproductive organs were observed after administration of **soybean oil** at a dose of 4000 mg/kg body weight and day (Hammond et al. 2008; see Section 5.2.2).

In a 4-generation study in Wistar and Long Evans rats that was published in 1944, the animals were given feed containing 2% (and 8% shortening), 5% (and 5% shortening) or 10% **lard**. Another group was fed a mixture of corn oil and shortening (no other details) and a control group was given untreated feed. Growth was similar in all groups. In all treatment groups, the dams exhibited a loss of body weight during lactation and nursed fewer offspring (pooled data for all treatment groups). The body weights of the dams increased when they were separated from their offspring. Lard was additionally available ad libitum and the animals ingested about 8 g of lard each day. This did not improve lactation and the offspring were killed by the dams during the lactation phase. The authors concluded from these findings that large quantities of lard interfered with the uptake of other feed constituents (no other details; CIREP 2001; FDA 1976). In a study of reproductive toxicity in 2-month-old female rats that was published in 1940, 2 animals of one litter

were fed bread, milk and water. Three females of the same litter were additionally fed 4 to 5 g of lard per day (80 g of lard or more/kg body weight and day). The animals fed with lard ate less and lost considerable weight. Additionally, they developed oedema in several areas. All 5 dams had offspring. The offspring of the animals fed with lard were stunted and had fatty livers. These findings were confirmed by the results of a similar experiment (FDA 1976).

5.5.2 Developmental toxicity

A teratogenicity study investigated **palm oil** (standard commercial product) in albino rats (8 to 11 per group). In addition to the standard feed, the rats were given 1, 2 or 3 ml of palm oil by gavage from gestation days 5 to 15 (about 4450, 8900 or 13 350 mg palm oil/kg body weight and day at a body weight of 200 g and a palm oil density of 0.89 g/cm^3 (NCBI 2021 b)). The control group received only the standard feed. The dams in all treatment groups had lower body weight gains than the control dams. In the treatment groups, the number of resorptions, the number of dead foetuses and the incidence of malformations were increased in a dose-dependent manner. In comparison with the findings in the controls, the most common effect observed in the foetuses was growth retardation. The most common anomaly found in the high dose group was exencephaly, followed by eye defects and cleft palate. Eye defects and cleft palate were observed only in the foetuses of the group given a dose of 3 ml. On a foetal basis, the incidences determined in the control and treatment groups were, by increasing dose: 0/53, 2/48, 3/49, 5/55 for exencephaly, 0/53, 0/48, 0/49, 3/55 for eye defects and 0/53, 0/48, 0/49, 1/55 for cleft palate with growth retardation. No developmental anomalies were observed in the control group. The author suggested that the eye defects were similar to those caused by increased doses of vitamin A. The author therefore attributed the defects to the high levels of carotene in palm oil (32 to 48 mg/100 ml, corresponding to maximum carotene doses of 2.4, 4.8, 7.2 mg/kg body weight and day at a body weight of 200 g), as carotene is a precursor of vitamin A (Singh 1980). Neither the rat strain nor the composition or impurities of the test substance were described in detail. In addition, the carotene levels in the test substance were not determined by analysis, but taken from the literature. The study did not include a suitable control group, which is a requirement for studies with gavage administration. Neither an evaluation on a per litter basis, nor a statistical analysis was carried out. The highest administered volume per animal was 3 ml (equivalent to 15 ml/kg body weight at a body weight of 200 g). This is above the volume recommended for rats of about 10 ml per kg body weight (Diehl et al. 2001). In high doses, oils have a laxative effect, which may lead to an insufficient supply of minerals. The dams in the study were in a poor general state of health and had diarrhoea. F344 rats given 128 mg vitamin A palmitate had an increased incidence of malformations; these were not observed at a dose of 32 mg/kg body weight and day (Hayes et al. 1981). Carotene is a precursor of vitamin A. However, it does not seem plausible to attribute the comparatively higher incidence of malformations induced at a carotene dose of 7.2 mg/kg body weight and day to the carotene content. Due to the considerable shortcomings listed above, the study has not been included in the evaluation.

5.6 Genotoxicity

5.6.1 In vitro

The mutagenic activity of **palm oil** was investigated by means of plate incorporation, pre-incubation and liquid incubation assay in the Salmonella typhimurium strains TA97, TA98, TA100, TA102, TA1537 and TA1538. After liquid incubation, a maximum 2-fold to 2.2-fold number of revertants was observed in the strain TA1537. Chromatographic fractionation of unrefined palm oil found that the mutagenic activity is caused by 3 fractions containing fatty acyl hydroperoxide. In all cases, the mutagenicity was abolished by adding catalase or a metabolic activation system. As the mutagenicity was abolished by catalase, this suggests that the mutagenic activity was moderated by hydrogen peroxide. No mutagenic effects were observed in the Salmonella typhimurium strains TA97, TA98, TA100, TA102 and TA1538 (Kensese et al. 1989). Another study investigated the mutagenic effects of palm oil in the Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538. The number of revertants was not doubled at the 2 test concentrations of 1 and 2 µl/plate (no other details; Sivaswamy et al. 1991). Therefore, palm oil was not found to be mutagenic in this test. In a bacterial mutagenicity assay carried out according to OECD Test Guideline 471 in the Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537, crude palm oil in concentrations of 50, 130, 500, 1500

and 5000 µg/plate did not induce mutagenic effects with and without the addition of a metabolic activation system. No cytotoxicity was observed up to the high concentration (ECB 2000).

5.6.2 In vivo

Soybean oil was investigated in a SMART (somatic mutation and recombination) wing spot test by exposing 2 strains of Drosophila melanogaster to concentrations of 6% and 12% in culture medium. In the standard cross, a higher frequency (1.04%) of spots per wing was detected in the 12% culture medium in comparison with the findings in the controls (0.40%). This effect was not observed in the other strain (norR). Per concentration, between 24 and 40 wings were assessed in the standard strain and 40 wings in the norR strain. The positive control, urethane, yielded a frequency of 1.53% total spots per wing. On the basis of these findings and the results obtained with other oils such as flax, wheat germ, sunflower, sesame and olive oil, an association was established between genotoxicity and the fatty acid composition. The higher the PUFA (polyunsaturated fatty acid) fraction and the lower the MUFA (monounsaturated fatty acid) fraction, the higher the percentage frequency of spots per wing. This finding was attributed to lipid peroxidation, which can lead to the formation of DNA adducts (Rojas-Molina et al. 2005). In another SMART wing spot test, the number of spots per wing was increased in a concentration-dependent manner (0.5% to 0.7%) in Drosophila melanogaster exposed to 6%, 12% and 24% soybean oil in 1% Tween 80 culture medium in comparison with the number of spots detected in the vehicle control group (0.25%). A total of 80 wings were examined per concentration. The positive control ethyl methanesulfonate yielded a frequency of 1.7% (Demir et al. 2012).

Three different samples of **palm oil** (in each case: supernatant, sediment and mixture of both) were examined in a test for chromosomal aberrations using the bone marrow cells from groups of 10 female BALB/c mice. The animals were given gavage doses of 4500 mg/kg body weight and day on 5 consecutive days. The control animals received corn oil; the positive controls were treated by intraperitoneal injection with a cyclophosphamide dose of 20 mg/kg body weight. The animals were sacrificed 24 hours after the last dose and the bone marrow from the upper thigh bones was then analysed. Per mouse, 100 metaphase bone marrow cells were examined for chromosomal aberrations (chromatid and chromosomal gaps, breaks, fragments and exchange) and 1000 metaphase cells were analysed to determine the mitotic index. The findings for chromosomal aberrations (overall and with gaps excluded) and the mitotic index that were determined in all treatment groups did not differ with statistical significance from the findings in the control group. The functioning of the test system was verified by the positive control (Oliveira et al. 1994).

The mutagenicity of a feed with high fat content was tested in vivo in the colon and small intestines. In both test systems, the Dlb-1 test and the lacl test (Big Blue™ mouse test), mice were fed a high-fat, isocaloric diet. The feed was formulated with 31% of either a mixture of beef tallow, butter and **lard** (about 62 000 mg/kg body weight and day, conversion factor of 0.2 for mice in subchronic studies (EFSA 2012)) and administered for up to 17 weeks or a mixture of corn oil, beef tallow, lard or butter and administered for 5 or 9 weeks. About half of the calories in the diet were administered in the form of fat. The body weights of the exposed animals did not differ from those of the control animals that were fed a standard diet without additives. None of the high-fat diets had any effects on the mutation frequencies. The authors concluded from these findings that uncooked fats are not mutagenic and are not initiators for the intestinal epithelium (Zhang et al. 1996).

5.7 Carcinogenicity

In a study of carcinogenicity and chronic toxicity, male Wistar rats were given refined **rapeseed oil** (containing 1% 22:1 fatty acids) for 107 to 110 weeks in daily doses of 11400 mg/kg body weight from weeks 1 to 5 and 3400 mg/kg body weight from weeks 88 to 90 (average: 4100 mg/kg body weight and day; no data for the other time periods). The tumour incidence was not higher than that determined in the animals fed partially hydrogenated soybean oil. The tumour incidences in all 5 exposure groups were in the range of the values obtained for the laboratory controls (see Section 5.2.2; Duthie et al. 1988).

A number of studies with female rats found that **palm oil** had an inhibitory effect on the development of mammary gland tumours; this effect was attributed to the high vitamin E content of palm oil (Johnson 2000).

When administered together with known initiators, food with a high **lard** content was found to induce a co-carcinogenic effect in rats, mice and hamsters (CIREP 2001; Ploeger et al. 2017; Rogers 1983). These findings are not relevant for exposure to triglycerides at the workplace.

The International Agency for Research on Cancer (IARC) classified the emissions produced at high temperatures by household animal and vegetable oils as carcinogenic in animal studies (IARC 2010). No conclusions can be drawn about the initial substances based on the findings for emissions generated by heating.

6 Manifesto (MAK value/classification)

As triglycerides are generally viscous oils with a low vapour pressure, exposure is expected to occur only in the form of an aerosol and not as a vapour. As is the case with white mineral oil, this can lead to the accumulation of macrophages and the formation of microgranulomas in the lungs. However, inhalation studies are not available for any of the substances. Systemic toxicity is low and only becomes detectable in the gram/kg body weight range.

MAK value. Repeated inhalation exposure to mineral oils such as white mineral oil leads to overloading of the lungs (Hartwig and MAK Commission 2017 b). Whereas mineral oils do not undergo hydrolysis, triglycerides are hydrolysed in the alveolar macrophages. However, once the capacity for hydrolysis is exceeded, these substances may likewise cause lung overload. The limit for hydrolysis is not known. Therefore, it is unclear at which concentration an overload effect is to be expected.

A provisional MAK value of 5 mg/m^3 R (respirable fraction) has been derived for the triglycerides in analogy to the value established for white mineral oil. In the lungs, triglycerides of vegetable and animal origin cause similar effects to those induced by mineral oil, but they are less marked. Therefore, setting the MAK value at 5 mg/m^3 R represents a conservative approach. This concentration will not be reached at workplaces through exposure to metal-working fluids as long as the corresponding technically-based limit value of 10 mg/m^3 I (inhalable fraction) is not exceeded. The amount of triglycerides expected to be taken up at the workplace through inhalation and dermal exposure is several orders of magnitude lower than the amount ingested with food. If the technically-based limit value for metal-working fluids of 10 mg/m^3 I is observed, an intake of 100 mg (10 m^3/8 hours, 100% absorption) is calculated for this workplace, corresponding to 1.4 mg/kg body weight and day at a body weight of 70 kg. Even for a scenario involving exposure to only triglyceride aerosol at very high concentrations, absorption by inhalation would only be in the mg/kg body weight range. In contrast, the recommended dietary intake is in the gram/kg body weight range (DGE 2015).

Even if the aerosol of the metal-working fluid were composed of erucic acid, the dose of 1.4 mg/kg body weight would be far below the NOAEL of 700 mg/kg body weight determined after the exposure of pigs and rats to erucic acid (EFSA 2013). Therefore, rapeseed oil containing erucic acid is not expected to induce systemic effects.

Peak limitation. The effects on the lungs are cumulative and late occurring (Hartwig and MAK Commission 2017 b); therefore, the substances have been classified in Peak Limitation Category II. In analogy to the factor established for pharmaceutical white mineral oil and the polyalphaolefins, an excursion factor of 4 has been set for peak limitation, as very high short-term concentrations may lead to changes in the distribution behaviour in the alveoli and thus also the dwelling time. In this case, the formation of microgranulomas in the lungs must be prevented (Hartwig 2011, available in German only).

Prenatal toxicity. There are no developmental toxicity studies available for the triglycerides that were carried out according to currently valid test guidelines.

The approach taken for the MAK value, namely, to carry out the assessment on the basis of the findings reported for pharmaceutical white mineral oil, cannot be used for developmental toxicity because of the potential effects of the triglycerides.

Formally, as there are no developmental toxicity studies available, the triglycerides would be assigned to Pregnancy Risk Group D.

However, fats are one of the main constituents of the human diet. The EFSA recommends a total fat intake of 20% to 35% of the daily energy intake (EFSA 2010). For a 25 to 51-year-old woman, 30% of the daily energy intake would correspond to a total daily intake of 63 g of fat, assuming a reference value for energy intake of 1800 kcal and low levels of physical activity (a physical activity level of 1.4) (DGE 2015).

If a woman is exposed to triglycerides at the level of the MAK value of 5 mg/m^3 R, it is calculated that she will take up 50 mg, equivalent to 0.8 mg/kg body weight and day (assuming 10 m^3/8 hours, 100% absorption, body weight of 60 kg). Even allowing for additional absorption of the inhalable fraction, exposure by inhalation would still be several orders of magnitude below the recommended total fat intake of 63 g/day; this is equivalent to 1050 mg/kg body weight and day at a body weight of 60 kg.

Moreover, in view of their structure, the main degradation products of vegetable and animal oils, such as monounsaturated oleic acid, gadoleic acid and palmitoleic acid, diunsaturated linoleic acid, triunsaturated linoleic acid and the saturated fatty acids palmitic acid, stearic acid and myristic acid, are not expected to induce teratogenic effects.

In addition to the direct effects on the foetus, secondary effects may likewise occur if hypoxia develops as a result of overloading of the lungs of the dam. Although there is no evidence of these types of effects for the triglycerides, data for other viscous oils do exist. In rats, rabbits, mice, gerbils and dogs, clinical signs of hypoxia such as cyanosis were not observed after inhalation exposure for 12 to 24 months to mineral oil in concentrations up to 100 mg/m^3 (Stula and Kwon 1978; Wagner et al. 1964). After rats were exposed by inhalation for 13 weeks to an oil mist generated from a light lubricating oil in a concentration of 1500 mg/m^3, lung function tests yielded findings outside the normal range in the form of an increased end-expiratory volume (Selgrade et al. 1990). In a number of studies, the end-expiratory lung volume was increased after hypoxia was experimentally induced in rats (Bonora and Vizek 1999). Assuming that the increased end-expiratory volume in the rats of the 13-week inhalation study is evidence of hypoxia, the LOAEC (lowest observed adverse effect concentration) for this effect is 1500 mg/m^3 and the NOAEC (no observed adverse effect concentration) is 500 mg/m^3. There is a 100-fold margin between the NOAEC and the MAK value of 5 mg/m^3. This provides adequate protection against the possible development of hypoxia induced by exposure to triglycerides.

The triglycerides have therefore been classified in Pregnancy Risk Group C.

Carcinogenicity. In a carcinogenicity study in male Wistar rats, no carcinogenic effects were observed after feeding the animals refined **rapeseed oil** in an average dose of 4100 mg/kg body weight and day (Duthie et al. 1988). Carcinogenicity studies were not carried out with the other substances.

In view of their structure, none of the substances are expected to cause carcinogenicity. For this reason, the triglycerides have not been classified in any of the categories for carcinogenic substances at the workplace.

Germ cell mutagenicity. **Palm oil** did not cause mutagenic effects in bacterial mutagenicity tests (ECB 2000; Johnson 2000; Kensese et al. 1989). After liquid incubation, a maximum 2-fold to 2.2-fold number of revertants was induced in the strain TA1537. Other studies attributed the mutagenic activity to acyl hydroperoxide (Kensese et al. 1989). Two SMART wing spot tests in Drosophila melanogaster found that **soybean oil**, administered in culture medium, slightly increased the number of spots per wing in comparison with the number of spots found in the controls (Demir et al. 2012; Rojas-Molina et al. 2005).

Palm oil given to mice orally at 4500 mg/kg body weight and day did not induce chromosomal aberrations in the bone marrow cells (Oliveira et al. 1994).

In two in vivo test systems, the Dlb-1 test and the lacl test (Big Blue™ mouse test), a mixture of beef tallow, butter and **lard** did not induce mutagenic effects in the colon and small intestines when administered with the feed at a dose of about 62 000 mg/kg body weight and day (Zhang et al. 1996).

The vegetable and animal oils are not expected to induce genotoxic effects based on the structure of the triglycerides and fatty acids these contain.

Therefore, the substances have not been classified in any of the categories for germ cell mutagens.

Absorption through the skin. Quantitative data for absorption through the skin are not available. Model calculations cannot be applied because of the complex and variable composition of the triglycerides. The dermal LD_{50} for rapeseed oil was above 2000 mg/kg body weight. As triglycerides are regularly ingested via the diet in the gram/kg body weight range, systemic effects are not expected to occur even at very high penetration rates. For this reason, the triglycerides evaluated in this documentation have not been designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. No positive findings in humans or from animal studies are available that would suggest that the triglycerides or the oils evaluated in the present documentation (for which there are diverse sources of topical exposure) have the potential to induce contact sensitization. Studies that investigated the induction of gastrointestinal symptoms in persons sensitized to soy protein, mostly children, are available only for soybean oils. The studies found that refined soybean oils do not induce sensitizing effects in these persons. There are no studies available that investigated the induction of sensitizing effects on the airways by the oils. However, it can practically be ruled out that the very low protein fraction in the oils will lead to sensitization of the airways or allergic reactions, also in view of the maximum possible level of exposure via the breathing air. In addition, there are no findings of protein contact dermatitis or urticaria induced by topical application of the evaluated oils that would serve as evidence of possible sensitization of the airways after percutaneous absorption. For this reason, the triglycerides and the evaluated oils that contain triglycerides have not been designated with "Sh" or "Sa" (for substances which cause sensitization of the skin or airways). However, it may be necessary to examine the protein content of crude, unrefined rapeseed or soybean oils separately because these oils may contain a much higher protein fraction.

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (www.dfg.de/mak/conflicts_interest) ensure that the content and conclusions of the publication are strictly science-based.

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