White mineral oil, pharmaceutical

MAK Value Documentation

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DOI: 10.1002/3527600418.mb804247kske5917

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated pharmaceutical white mineral oil which is a grade of white mineral oil [8042-47-5] considering all toxicological endpoints. Available publications are described in detail. In addition to studies with white mineral oils, studies with other highly refined mineral oils are used. Critical effect is lung toxicity which is observed as microgranulomas in two long-term studies with rats and dogs at a respirable aerosol concentration of 100 mg/m³ with a NOAEC of 5 mg/m³. A MAK value of 5 mg/m³ has been set as the respirable fraction (R). Since the critical effect is a long-term effect on the lung, Peak Limitation Category II is designated, with an excursion factor of 4. The NOAEC and the oral NOAEL for developmental toxicity of white mineral oil in rats are 1000 mg/m³ and 5000 mg/kg body weight, respectively. The differences between the MAK value and the NOAEC and that of the oral NOAEL scaled to a concentration at the work place are sufficiently large, so that damage to the embryo or foetus is unlikely when the MAK value is not exceeded. Pharmaceutical white mineral oil is therefore classified in Pregnancy Risk Group C. Highly refined mineral oils are neither genotoxic nor carcinogenic. Skin contact is not expected to contribute significantly to systemic toxicity. Numerous studies where purified mineral oil and petrolatum are used as a vehicle show no sensitization in humans and animals. The same is expected for pharmaceutical white mineral oil.

Keywords

white mineral oil; low-viscosity paraffin; high-viscosity paraffin; mechanism of action; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; irritation; allergenic effects; reproductive toxicity; fertility; developmental toxicity; genotoxicity; carcinogenicity; peak limitation; prenatal toxicity; germ cell mutagenicity; absorption through the skin; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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MAK value (2014)	**5 mg/m³ R (respirable fraction)**
Peak limitation (2014)	**Category II, excursion factor 4**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2014)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**
BAR/BLW/EKA	**–**
Synonyms	low-viscosity and high-viscosity paraffin
Chemical name	–
CAS number	8042-47-5
Structural formula	mixture of saturated C15 – C50 hydrocarbons (ECHA 2014)
Molar mass	about 212 to 702 g/mol
Melting point	no data (liquid)
Boiling point at 1013 hPa	260 – 600°C (ECHA 2014)
Density at 15°C	0.81 – 0.894 g/cm³ (ECHA 2014)
Vapour pressure at 20°C	< 0.001 hPa (highly refined base oil) (ECHA 2014)
log K_{OW} [1)]	> 6 (calculated; ECB 2000) 5.6 – 25 (calculated for C15 – C50; ECHA 2014)
Solubility	1.8×10^{-1} – 7.1×10^{-21} mg/l water (calculated for C15 – C50; ECHA 2014)
Stability	no data

1) octanol/water partition coefficient

Production	By intensive treatment of a petroleum fraction with sulfuric acid and oleum, or by hydrogenation or a combination of hydrogenation and acid treatment. Additional washing and treatment steps can be included in the production process (ECHA 2014)
Purity	Pharmaceutical white mineral oil is of high purity and complies with the purity requirements of the European Pharmacopoeia
Impurities	Technical-grade white mineral oils are often hydrated only once and still contain traces of aromatic hydrocarbon compounds, which are carcinogenic. Medical-grade white mineral oils are colourless, odourless and tasteless; they do not contain any aromatics or sulfur compounds (Sommerhoff GmbH 2013)
Uses	As lubricants, insecticides, in production oils for plastics in the food industry, in pharmaceutical products and cosmetics, release agents, anticorrosives, dielectrics in transformers (Sommerhoff GmbH 2013)

White mineral oil is a component of mineral oil, and is evaluated as such (see also SCOEL 2011). This evaluation is based on the documentation for "polyalphaolefins" (documentation "Polyalphaolefine" 2011, available in German only), on reviews by ATSDR (1997), SCOEL (2011) and DECOS (2011), in which the relevant studies of mineral oils are described, and on the publicly available registration data in the REACH databank (ECHA 2014). For highly refined mineral oils, an OEL (8-hour occupational exposure limit) of 5 mg/m^3 has been established by SCOEL (2011) for the inhalable fraction. From the same database, DECOS (2011) derived an occupational exposure limit of 1.6 mg/m^3.

White mineral oil products are classified according to their viscosity, which increases with the C number, the crude oils used—and thus the ratio of paraffinic to naphthenic alkanes they contain—and the purification and production processes involved. For these different types, there are different CAS numbers.

For applications in the food industry, low-viscosity white mineral oils are defined as having an average molar mass of up to 480 g/mol, medium-viscosity white

mineral oils a molar mass of 480 to 500 g/mol and high-viscosity oils a molar mass of above 500 g/mol (EFSA 2009, 2013).

1 Toxic Effects and Mode of Action

The acute toxicity of highly refined mineral oils is relatively low. With increasing chain length, they are less readily absorbed and metabolized after ingestion. In long-term studies with rats and dogs, they induced adverse effects in the lungs in the form of microgranulomas at concentrations of 100 mg/m^3 and above. Single applications to the skin of rabbits were found to be non-irritative and non-sensitizing; single instillations in the eyes were not irritative. Skin irritation was observed in rats after repeated application. In several studies, highly refined mineral oils were not found to be genotoxic or carcinogenic. White mineral oil did not have any toxic effects on development in rats after oral doses of up to 5000 mg/kg body weight and after inhalation exposure to a concentration of 1000 mg/m^3.

2 Mechanism of Action

Mineral oils can accumulate in the lungs, where, as a result of incomplete phagocytosis by macrophages, they cause inflammatory reactions (exogenous lipid pneumonia) and microgranulomas, and even fibrotic changes (SCOEL 2011).

Oral studies with white mineral oils of low viscosity (low C number) revealed an accumulation of white mineral oil components in the liver and lymph nodes of rats. Especially female F344 rats also develop microgranulomas as a result of inflammation in the liver. Other rat strains, such as SD or Long Evans rats, are less sensitive (Section 5.2.2). These effects were not observed in other species. They are of little relevance for humans; although microgranulomas may occur after the ingestion of mineral oil, these do not develop into lesions of any clinical significance (Fleming et al. 1998). In addition, the F344 rat appears to be particularly sensitive. This effect does not occur with medium and high-viscosity white mineral oils, as these have longer molecule chains and are less readily absorbed after ingestion (Section 3.1). Nevertheless, also with medium and high-viscosity white mineral oils, histiocytosis is induced in the mesenteric lymph nodes of F344 rats. This was, however, evaluated as an exposure marker and not regarded as adverse, as it did not develop any further over time (EFSA 2009, 2013).

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

Absorption by inhalation probably takes place via macrophage-mediated clearance. The following evidence for this mechanism can be found for the hydrocarbons from

mineral oils in hydraulic fluids: oil was found in the alveolar macrophages, mediastinal lymph nodes, lymphatic channels of the lungs, and in the pleura of mice, rats and rabbits exposed to 63 000 mg/m^3 of a diesel-engine lubricating oil aerosol (particle sizes of 0.34 to 1.45 μm) for up to 343 days. Chemical analysis of the lung and liver tissue from the exposed mice revealed an oil content of 0.13% and 0.03%, respectively, but no oil in the control animals (ATSDR 1997).

Mineral oils were found to accumulate in the lungs of humans and animals after inhalation or ingestion. Once absorbed, they are distributed preferentially in the liver and adipose tissues, are slowly metabolized, and are eliminated via the bile with the faeces. This is also to be expected for white mineral oil (ATSDR 1997). The mineral oil components found in the human liver were observed in connection with their use as laxative or after dietary intake (Fleming et al. 1998).

In rats, 60% of C14 hydrocarbons, 5% of C28 hydrocarbons and essentially 0% of hydrocarbons > C32 were found to be orally absorbed (DECOS 2011). Medium and high-viscosity white mineral oils which contain only a low amount of hydrocarbons < C30 are orally absorbed to about 3% by F344 rats. By contrast, eicosanylcyclohexane (C26), which can be considered representative of low-viscosity white mineral oil, is excreted, depending on the dose, in amounts of up to 25% with the urine in the form of acid metabolites by female SD and F344 rats after oral administration. F344 rats eliminate the metabolites somewhat more slowly than SD rats and have a higher AUC (area under the curve) in blood (Halladay et al. 2002). This means that F344 rats accumulate orally administered eicosanylcyclohexane (Halladay et al. 2002) and low-viscosity white mineral oil in the liver to a markedly greater extent than do SD rats (Firriolo et al. 1995).

In monkeys, 85% to 99% of a subcutaneously injected aqueous white mineral oil emulsion remained at the site of application for one week (DECOS 2011). Therefore, epicutaneous application should result in even poorer absorption. For white mineral oil itself, no data are available; however, the penetration of only about 1% was demonstrated for C16 to C28 alkanes in several in vitro and in vivo studies with different species (Nash et al. 1996).

There are no data available for the solubility of the substance in water. The calculated log K_{OW} is outside the range valid for the models used to calculate skin penetration (maximum value log K_{OW} 6), so that this cannot be calculated.

3.2 Metabolism

The hydrocarbons of mineral oils containing longer-chain molecules are gradually metabolized to various lipids (fatty acids or triglycerides) (ATSDR 1997).

4 Effects in Humans

Oral or inhalation exposure to lipid-like products can induce exogenous lipid pneumonia in adults. In a retrospective study, 4 of 44 cases were associated with inhala-

tion exposure to mineral oil products in occupational settings. Further cases have been observed after occupational exposure to oil spray, engine oil spray, cutting oil, oil mist, paint aerosols and rape seed oil. However, no exposure data are available (SCOEL 2011).

One study reported lipid pneumonia after exposure to mineral oil concentrations of less than 5 mg/m^3. In this case there was also simultaneous exposure to a water soluble coolant of unknown composition (Cullen et al. 1981).

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

Highly refined white mineral oil is of low toxicity after short-term inhalation, oral and dermal exposure. Mild inflammatory reactions occurred in the lungs of mice after exposure to concentrations of 200 mg/m^3 for 4 hours. The oral LD_{50} values (species not specified) are above 5000 mg/kg body weight, the dermal LD_{50} values for rabbits are above 2000 mg/kg body weight (DECOS 2011).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

After repeated inhalation of highly refined mineral oil aerosols, the lung is the target organ in dogs, rats, mice, rabbits and hamsters (Table 1; see documentation "Polyalphaolefine" 2011, available in German only). After exposure of rats for 4 and 13 weeks, a no observed adverse effect concentration (NOAEC) of 50 mg/m^3 was reported (Dalbey 2001; Dalbey et al. 1991), and after exposure of rats and dogs for 12 to 24 months, a NOAEC was given of 5 mg/m^3. With a NOAEC of 100 mg/m^3, mice, rabbits and hamsters are less sensitive. At these doses oil is deposited in the lungs, (oil-laden) macrophage accumulation occurs and sometimes hilar lymph nodes laden with oil or macrophages are observed. These findings do not have adverse effects on the lungs and are considered a physiological reaction. Adverse effects were found in the form of microgranulomas in the lungs of dogs and rats after exposure to 100 mg/m^3 (Stula and Kwon 1978; Wagner et al. 1964).

On account of their common chemical structure (saturated hydrocarbons), the molecule size ($\geq$ C15), the poor water solubility and the absence of functional groups of highly refined mineral oils and white mineral oil, it is to be assumed that the purely physical effect on the lungs of these substances is the same after repeated inhalation (documentation "Polyalphaolefine" 2011, available in German only).

Table 1 Effects of mineral oils after repeated inhalation exposure

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 10 ♂/♀	**4 weeks**, 0, 50, 210, 1020 mg/m³ (MMAD about 0.8–1 µm, GSD 2) **white mineral oil (18 mm²/s at 40°C)** 6 hours/day, 5 days/week	**50 mg/m³ and above**: 20/20 with 1–2 foam cells **210 mg/m³ and above: LOAEC**, ♀: wet lung weights ↑ **1020 mg/m³**: 20/20 with 1–6 foam cells, 19/20 with slight infiltration of polymorphonuclear neutrophils in the alveoli, 19/20 with accumulation of macrophages in tracheobronchial lymph nodes, ♂: wet lung weights ↑	Dalbey et al. 1991
rat, Sprague Dawley, 6–15 ♂, in some cases also ♀	**13 weeks**, 0, 200, 500, 1500 mg/m³ (MMAD about 1 µm) **oil mist from light-weight lubricating oil** 3.5 hours/day, 4 days/week 4-week recovery period	**200 mg/m³**: **LOAEC** **200 mg/m³ and above**: accumulation of macrophages in alveoli (concentration-dependent degree of severity), persistent, mild inflammatory oedema, proteins in lavage fluid ↑ **500 mg/m³ and above**: proteins in lavage fluid ↑, polymorphonuclear leukocytes ↑, wet and dry lung weights ↑ **1500 mg/m³**: end expiratory volume (EEV) ↑, wet and dry lung weights ↑ (not reversible during recovery period)	Selgrade et al. 1990
rat, Sprague Dawley, 15 ♂/♀	**13 weeks**, 0, 50, 150, 400–520 mg/m³ (MMAD about 1–2 µm) **3 formulations mainly from superrefined mineral oil (cutting oil, gear oil and commercial engine oil)** 6 hours/day, 5 days/week	**50 mg/m³**: **NOAEC** **150 mg/m³**: **LOAEC** **150 mg/m³ and above**: macrophage accumulation in pulmonary alveoli and alveolar walls, slight thickening of the alveolar walls (due to macrophages and infiltration of mixed cells), slight epithelial hyperplasia, wet lung weights ↑, pulmonary hydroxyproline ↑	Dalbey 2001

Table 1 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 4–20 ♂/♀	**12–24 months**, 0, 5, 100 mg/m³ (MMAD about 0.9–1.1 µm)	**rat, dog** **5 mg/m³**: **NOAEC**	Stula and Kwon 1978
dog, Beagle, 4 ♂	**mineral oil** and 1000 ml acetone/m³, (fibre yarn preparation) 6 hours/day, 5 days/week	**5 mg/m³ and above**: oil-laden macrophages in lungs and hilar lymph nodes (not adverse) **100 mg/m³**: microgranulomas in lung	
mouse, CD, 12–19 ♂ CAF/JAX, 17–27 ♂ **gerbil**, not specified, 2–9 ♂	**mineral oil composition: 70% low-viscosity paraffinic oil** Saybolt Universal Second [SUS] at 38°C = 48–52 (kinematic viscosity about 10 mm²/s at 40°C), **30% surfactant, buffer and other substances** (16% plant oil, 11% tensides, 3% resins) **exposure time and recovery period** rat: 12 months (+ 10 months) dog: 24 months; mouse: 12 months gerbil: 12 months (+ 2 months)	**mouse and gerbil** **5 mg/m³ and above**: only few oil-laden macrophages in lungs and hilar lymph nodes **100 mg/m³**: **NOAEC**	

Table 1 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, Holtzman Sprague Dawley, 80–85 ♂ **dog**, mixed breed, 9 ♂ **mouse**, CF-1, 60 ♂ **rabbit**, Dutch, 23–26 ♂ **hamster**, Syrian golden hamster, 106–112 ♂	**12–24 months**, 0, 5, 100 mg/m^3 pure, white naphthenic mineral oil 5 hours/day, 6 days/week MMAD 1.3 µm SUS = 85–95 C25–C30 **exposure times and interim necropsies**: rat: 6, 12, 16 months; dog: 6, 12, 18, 24 months; mouse: 12 months at 5 mg/m^3 or 12 and 16 months at 100 mg/m^3; rabbits: 6, 12, 18 months; hamster: 6, 12, 15 months	**rat, dog** **5 mg/m^3: NOAEC** **rat** **100 mg/m^3**: lungs: oil-laden macrophages, alkaline phosphatase and Mg-activated alkaline phosphatase ↑ (after 9 months and later) **dog** **5 mg/m^3 and above**: oil deposits in alveoli and hilar lymph nodes (after 6 months and later) **100 mg/m^3**: lungs: alkaline phosphatase ↑ (after 12 months and later), Mg-activated alkaline phosphatase ↑ (18 months), lipid granuloma formation (12 months) **hamster, rabbit, mouse** **100 mg/m^3: NOAEC** **hamster** **100 mg/m^3**: lungs: alkaline phosphatase and Mg-activated alkaline phosphatase ↑ (only at interim necropsy after 9 months); only few oil-laden macrophages in the lungs (15 months) **rabbit, mouse** **5 mg/m^3 and above**: only few oil-laden macrophages in the lungs; no effects on body weight gains; no haematological effects; no unusual findings in the breathing function test (carried out with rabbits only)	Wagner et al. 1964

GSD: geometric standard deviation; MMAD: mass median aerodynamic diameter

5.2.2 Oral administration

In medium-term studies with low-viscosity white mineral oils in rats, the accumulation of white mineral oil components and microgranulomas in the liver and mesenteric lymph nodes, and histiocytosis in the mesenteric lymph nodes were observed. The doses were 160 and 1500 mg/kg body weight; SD rats accumulated markedly less white mineral oil and were less sensitive than F344 rats (Firriolo et al. 1995). The particular sensitivity of female F344 rats was confirmed in another study with several low-viscosity mineral oils, in some cases down to dose levels of as little as 20 mg/kg diet (about 1.5 mg/kg body weight) (Smith et al. 1996). In contrast, no such effects were found in Long Evans rats up to doses of 120 mg/kg body weight, nor in dogs up to about 50 mg/kg body weight and day (Smith et al. 1995) or rabbits and guinea pigs (Firriolo et al. 1995). The lipogranulomas and histiocytosis in the mesenteric lymph nodes are considered to be of little relevance for humans (see Section 2).

In a 2-year study with interim necropsies after 3, 6 and 12 months in which two different medium and high-viscosity white mineral oils were used (70.4 mm^2/s at 40°C = 8.97 mm^2/s at 100°C or 100.3 mm^2/s at 40°C = 11.3 mm^2/s at 100°C), no adverse effects were found in F344 rats at the highest dose tested of 1200 mg/kg body weight (Trimmer et al. 2004). The histiocytosis in the mesenteric lymph nodes observed in this study was regarded as an exposure marker and not considered to be adverse (see Section 2).

5.2.3 Dermal application

In a 90-day study carried out according to OECD Test Guideline 411, white mineral oil doses of 0, 125, 500 or 2000 mg/kg body weight and day were administered daily for 13 weeks to groups of 10 SD rats per sex and dose. The viscosity of the white mineral oil was 16 mm^2/s at 40°C and thus low. Skin irritation occurred at doses of 125 mg/kg body weight and above. A NOAEL (no observed adverse effect level) for local effects could, therefore, not be obtained. The decrease in body weight gains of the males was statistically significant at 500 mg/kg body weight and above, and also in the females at 2000 mg/kg body weight. There were no effects on urine parameters, clinical chemistry, clinical symptoms, mortality, food consumption or organ weights, and the results of the haematological and histopathological examinations were normal. A NOAEL of 2000 mg/kg body weight and day was given for systemic effects (ECHA 2014). In another description of the study it is stated that exposure took place on 5 days a week instead of daily, and that although samples were taken for histopathology these were not evaluated. For this reason, no systemic NOAEL can be given for the study (API 2011 a). Although the reduction in body weight gains was treatment-related, it could also be a secondary effect of the skin irritation, or a disturbance in thermoregulation as a result of the dermal application of a large volume of the test substance, as reductions in body weight gains have not been

found in studies with oral administration. It is therefore presumably not a genuine systemic effect (API 2011 b).

5.3 Local effects on skin and mucous membranes

The irritation potential of highly refined mineral oils to the skin and eyes of rabbits is very low (DECOS 2011). In two studies carried out with rabbits according to OECD Test Guidelines 404 and 405, white mineral oil had no irritative effects on the skin (irritation score 0/8) or in the eyes (irritation score 0.22/20 for the conjunctiva and 0 for the cornea and iris) (ECHA 2014).

5.4 Allergenic effects

In the database of the ECHA, two Bühler tests with undiluted mineral oils are listed, both of which yielded negative results. In one of the tests, none of the 10 animals produced a reaction; in the second, a very weak reaction (irritation score 0.1) was observed in only one animal. In a third Bühler test, in which induction was carried out with 75% of the substance "in paraffin oil", none of the 10 animals reacted to the challenge treatment with 25% of the substance, but 6 of 10 and 5 of 10 animals reacted 24 and 48 hours, respectively, after repeated challenge treatment with the same concentration (ECHA 2014). However, no information is given for the reactions after the second challenge in the control group; therefore this finding cannot be included in the evaluation.

As purified mineral oil or paraffin oil has been used as the vehicle in numerous animal studies, even for intradermal applications, without leading to sensitization, sensitization resulting from contact with pharmaceutical white mineral oil is not to be expected. The skin sensitizing potential of these types of purified paraffin oils is to be regarded as the same as that of (white) petrolatum, which is likewise not skin sensitizing and therefore used as the vehicle also in patch tests with humans (Schnuch et al. 2006).

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

White mineral oil was used as the vehicle control in two studies in which groups of 72 female and 36 male rats were given gavage doses of 5 ml/kg body weight and day (about 4250 mg/kg body weight) on 5 days a week for 13 weeks. Thereafter, the animals were mated for 10 days and the females were kept unexposed up to day 21 post partum. There were no unusual findings regarding cycle length, fertility, number of pups and postnatal development. The number and type of external malformations was similar to those occurring spontaneously in this strain of rat (McKee et al. 1987 a).

In a study carried out according to OECD Test Guideline 421 in SD rats, no relevant effects on reproduction were found compared with untreated control animals after dermal application of 1 ml white mineral oil/kg body weight and day (about 850 mg/kg body weight) (Schreiner et al. 1997).

In a one-generation study similar to OECD Test Guideline 415 carried out with SD rats, no adverse effects on fertility and development were found after dermal application of 0, 125, 500 or 2000 mg white mineral oil/kg body weight and day. Skin irritation occurred in all treated male animals (ECHA 2014).

5.5.2 Developmental toxicity

In a developmental toxicity study similar to OECD Test Guideline 414, 20 SD rats were exposed in whole body exposure chambers to a white mineral oil aerosol concentration of 1000 mg/m^3 (MMAD 1.2 µm) from gestation days 6 to 19 for 6 hours a day. Neither maternal toxicity nor embryotoxicity or teratogenicity were found (ECHA 2014).

In a developmental toxicity study similar to OECD Test Guideline 414, 20 SD rats were given gavage doses of 5000 mg white mineral oil/kg body weight, daily from days 6 to 19 of gestation. Neither maternal toxicity nor embryotoxicity or teratogenicity were found (ECHA 2014).

White mineral oil was used as the vehicle control in two studies in which 49 and 25 SD rats, respectively, were given daily gavage doses of 5 ml/kg body weight (about 4250 mg/kg body weight) from gestation days 6 to 19. The number of implantations was 12.0 and 11.3 per litter and the number of resorptions 0.47 and 0.06, respectively. One malformed foetus was found in 3 of 49 and in 3 of 25 litters, respectively (McKee et al. 1987 b).

No developmental toxicity was observed after dermal exposure to lubricating base oils in doses of 2000 mg/kg body weight and day from gestation days 1 to 19 (DECOS 2011).

5.6 Genotoxicity

Highly refined mineral oils were not found to be genotoxic in Salmonella mutagenicity tests, mouse lymphoma tests, bone marrow cytogenetic tests and micronucleus tests (no other details; DECOS 2011).

5.7 Carcinogenicity

In long-term studies with highly refined mineral oils in rats and dogs, the tumour incidence was not increased up to concentrations of 100 mg/m^3. No treatment-related tumours were found after oral administration, dermal application, or subcutaneous and intraperitoneal injection (DECOS 2011).

6 Manifesto (MAK value/classification)

The target organ is the lung.

MAK value. On account of their common chemical structure (saturated hydrocarbons), the molecule size (> C15), the poor water solubility and the absence of functional groups, pharmaceutical white mineral oil and highly refined mineral oils are expected to have the same local effects on the lungs after repeated inhalation. Therefore, studies with repeated inhalation exposure to highly refined mineral oils are used to derive a MAK value for pharmaceutical white mineral oil.

After repeated inhalation of respirable aerosols of highly refined mineral oils, the lung is the target organ in dogs, rats, mice, rabbits and hamsters. A NOAEC of 50 mg/m^3 was reported after the inhalation exposure of rats for 13 weeks, and a NOAEC of 5 mg/m^3 after the inhalation exposure of rats and dogs for 12 and 24 months, based on microgranulomas in the lungs found at 100 mg/m^3. As the difference between the NOAEC of 5 mg/m^3 from long-term studies in rats and dogs (also taking into consideration the NOAEC of 50 mg/m^3 after 13-week exposure of rats) and the lowest observed adverse effect concentration (LOAEC) of 100 mg/m^3 is sufficiently large, and as no great interindividual variation as regards the critical effect (overloading of the lungs), and also no relevant systemic uptake is to be expected, a MAK value of 5 mg/m^3 R has been established for pharmaceutical white mineral oil.

Peak limitation. Because the effects are cumulative and late occurring, the substance is classified in Peak limitation category II. In analogy to polyalphaolefins (documentation "Polyalphaolefine" 2011, available in German only) an excursion factor of 4 is established for peak limitation.

Prenatal toxicity. In rats, neither inhalation exposure to white mineral oil concentrations of 1000 mg/m^3 nor oral doses of 5000 mg/kg body weight and day resulted in developmental or maternal toxicity. The following toxicokinetic data are taken into consideration for the extrapolation of this oral NOAEL to a concentration in workplace air: the corresponding species-specific correction value (1:4) for the rat, oral absorption of 5% (experimental determination for C28 hydrocarbons), the body weight (70 kg) and respiratory volume (10 m^3) of the person, and the assumed 100% absorption by inhalation. The concentration calculated from this is 438 mg/m^3. The 200-fold difference between the MAK value of 5 mg/m^3 R and the NOAEC for inhalation exposure, and the 88-fold difference between the MAK value and the calculated concentration in air are sufficiently large to allow the classification of pharmaceutical white mineral oil in Pregnancy Risk Group C.

Carcinogenicity and germ cell mutagenicity. Highly refined mineral oils are not genotoxic or carcinogenic, so that white mineral oil is not classified in one of the categories for either carcinogens or germ cell mutagens.

Absorption through the skin. The dermal LD_{50} for rabbits is greater than 2000 mg/kg body weight. In monkeys, 85% to 99% of a subcutaneously injected

aqueous white mineral oil emulsion remained at the site of application for one week. In vitro, the maximum amount of C16 and C25 aliphatics absorbed through the skin of humans and pigs was 1%. With epicutaneous application of white mineral oil it may therefore be expected that dermal absorption is very low and does not contribute to systemic toxicity, for which reason the substance is not designated with an "H" (for substances which are absorbed through the skin in toxic amounts).

Sensitization. Despite the exposure of humans to (pharmaceutical) white mineral oil, there are no clinical findings for skin and respiratory sensitization. There are also no reliable animal studies which provide evidence of sensitization of the skin. In addition, purified mineral oils are often used as the vehicle in experimental studies without sensitization being observed. Pharmaceutical white mineral oil is therefore not designated with either "Sa" or "Sh" (for substances which cause sensitization of the airways or skin).

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completed 26.02.2014