The MAK Collection for Occupational Health and Safety

Mineral oils (petroleum), severely refined

MAK Value Documentation – Translation of the German version from 2018

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)*

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Mineral oils (petroleum), severely refined

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

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated 4 severely refined mineral oils [92062-35-6, 72623-83-7, 92045-45-9, 92045-44-8] considering all toxicological endpoints.

These mineral oils are severely refined to eliminate olefins and carcinogenic polycyclic aromatic hydrocarbons. The 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). Severely refined mineral oils have been assigned to Peak Limitation Category II, because the lung effects are due to a cumulative overload and an excursion factor of 4 has been set. Severely refined mineral oils are not genotoxic and not carcinogenic after oral, dermal or subcutaneous application to rats and mice.

Developmental toxicity studies with a white mineral oil show a NOAEC of 1000 mg/m³ and a NOAEL of 5000 mg/kg body weight in rats. After toxicokinetic scaling, the differences of the resulting respective concentrations at the workplace to the MAK value are sufficient. Therefore, damage to the embryo or foetus is unlikely when the MAK value is observed and severely refined mineral oils are assigned to Pregnancy Risk Group C. Skin absorption is very limited and does not contribute to systemic toxicity. Severely refined mineral oils are not regarded as skin or respiratory sensitizers.

Keywords

mineral oils, severely refined; petroleum; lubricating oils, severely refined; light white mineral oil; hydrotreated bright stock-based lubricating oils; hydrotreated solvent-refined bright stock-based lubricating oils; 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

Author Information

[1] Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Department of Food Chemistry and Toxicology, Institute of Applied Biosciences, 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)

Mineral oils (petroleum), severely refined

MAK value (2017)	**5 mg/m³ R (respirable fraction)**
Peak limitation (2017)	**Category II, excursion factor 4**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2017)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**
Synonyms	lubricating oils, severely refined
Chemical name	light white mineral oil (petroleum), C > 12
CAS number	[92062-35-6]
Chemical name	hydrotreated bright stock-based lubricating oils (petroleum), C > 25
CAS number	[72623-83-7]
Chemical name	hydrotreated solvent-refined bright stock-based lubricating oils (petroleum), C > 40
CAS number	[92045-45-9]
Chemical name	hydrotreated bright stock-based lubricating oils (petroleum), C > 50
CAS number	[92045-44-8]
Formula	mixture of mainly saturated hydrocarbons
Molar mass	about 170–702 g/mol (C12–C50)
Melting point	no data (liquid)
Boiling point at 1013 hPa	> 300 °C at C > 15 (DECOS 2011)
Density at 15 °C	0.81–0.894 g/cm³ (ECHA 2016 a)

Vapour pressure at 20 °C	< 0.001 hPa (highly refined base oil) (ECHA 2016 a)
log K_{OW}[1)]	5.6–25 (calculated for C15–C50; ECHA 2016 a)
Solubility	$1.8 \times 10^{-1} - 7.1 \times 10^{-21}$ mg/l water (calculated for C15–C50; ECHA 2016 a)

This evaluation was carried out on the basis of the documentation "White mineral oil, pharmaceutical" 2015 and reviews by SCOEL (2011) and DECOS (2011) that describe the most important studies with mineral oils. No REACH datasets are currently available to the public for any of the four mixtures listed above, only for lubricating oils in general, which have the CAS number [74869-22-0] (ECHA 2016 b). The three lubricating oils discussed in this evaluation and white mineral oil were assessed by SCOEL together with pharmaceutical white mineral oil (CAS number [8042-47-5], C > 15) as representatives of the group of severely refined mineral oils. For this reason, also this documentation refers to the data for white mineral oils and other severely refined mineral oils.

Mineral oils are obtained by vacuum distillation of the residues remaining after crude petroleum oils are refined by atmospheric distillation. During this process, the residues are separated into distinct fractions with different viscosities based on differences in boiling points. These fractions are known as the mineral base oils. Depending upon the intended application, these can be further purified using a range of refining processes such as hydrotreatment and solvent extraction, which are used either alone or in combination. White mineral oils are obtained after additional acid treatment. The three lubricating oils discussed in this evaluation are derived from what is known as bright stock oil. Bright stock oil is a light viscous oil that has undergone two hydrogenation processes separated by a dewaxing process after the removal of the asphalt fraction from vacuum distillation residues. Severely refined mineral oils are used as lubricant base oils with and without other additives for a large number of industrial applications, including in automobiles, machines and cooling lubricants. As severely refined mineral oils have a high molar mass, their vapour pressure is low, which means that exposure to these substances occurs primarily in aerosol form. In the 1990s, concentrations at the workplace were in the range from 1 to 2 mg/m^3, analysed as the inhalable fraction, which is equivalent to a respirable fraction of around 0.5 to 0.8 mg/m^3 (DECOS 2011; SCOEL 2011).

Among other things, hydrotreatment reduces the double bonds of alkenes and aromatics. The product is then further purified after undergoing additional refining steps, including a second hydrogenation process. These processes are carried out primarily to remove polycyclic aromatic hydrocarbons (PAHs), thereby eliminating the carcinogenic potential (SCOEL 2011). The polycyclic aromatic hydrocarbon content is dependent upon the intensity of refining and can be approximated using the IP 346 method: a mineral oil is not considered carcinogenic if less than 3% of its mass can be extracted with dimethyl sulfoxide (DMSO). The DMSO extract is made

1) octanol/water partition coefficient.

up mainly of naphthenes, monoaromatics and polycyclic aromatic hydrocarbons. Skin painting tests in mice found that mineral oils containing less than 3% DMSO extract were not carcinogenic to the skin (CONCAWE 1994). A comparison revealed that skin carcinogenicity in mice correlated with the polycyclic aromatic hydrocarbon content and the mutagenic activity in the Salmonella mutagenicity test (Roy et al. 1988). For this reason, mineral oils containing more than 3% of substances extractable with DMSO are considered to be carcinogens in the EU and USA. This 3% limit as the cut-off value for classification as a carcinogen has been criticized because it is based on a tumour incidence of 4% in experimental animals for the differentiation of carcinogenic and non-carcinogenic mineral oils and the different mouse strains vary in their sensitivity (BfR 2018).

The four severely refined mineral oils discussed in this documentation are not classified as carcinogens because, unlike a large number of other mineral oils, severely refined mineral oils were studied for their carcinogenicity after oral and dermal exposure and no respective effects were found. It is assumed that these mineral oils have the same effects as pharmaceutical white mineral oil because the substances essentially only differ in the number of carbons. For this reason, this documentation does not include an in-depth discussion of all end points. Instead, reference is made to the respective documentation "White mineral oil, pharmaceutical" 2015 and in particular to the comprehensive compilation of data for mineral oils (DECOS 2011).

In humans, accumulations of mainly branched and cyclic alkanes from mineral oils were found in the lymph nodes, liver, fat and spleen. It is very likely that these were caused by the use of mineral oils in foods, the discharge of mineral oils from machines during food production or their transfer from materials used for packaging (EFSA 2012). The use of cosmetics may also have contributed (Barp et al. 2014).

1 Toxic Effects and Mode of Action

The longer the chain length or higher the number of carbon atoms, the less readily mineral oils are absorbed and metabolized after oral and dermal exposure. In studies with rats and dogs, severely refined mineral oils induced adverse effects in the lungs in the form of microgranulomas at concentrations of 100 mg/m^3 and above. They did not induce irritation of rabbit skin and eyes after single applications and did not have a sensitizing effect on the skin. In a number of studies, severely refined mineral oils were not found to be genotoxic or carcinogenic after oral or dermal exposure of rats and mice. The lung tumour incidence was not increased in long-term studies with inhalation exposure of rats and mice to a concentration of 100 mg/m^3. White mineral oil, a severely refined mineral oil that has undergone acid treatment, did not have toxic effects on development in rats given oral doses of up to 5000 mg/kg body weight or exposed by inhalation to a concentration of 1000 mg/m^3. No adverse effects on fertility were detected after oral or dermal exposure of rats to white mineral oil doses of around 4200 and 2000 mg/kg body weight and day, respectively.

2 Mechanism of Action

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

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

Absorption by inhalation probably takes place via macrophage-mediated clearance. This mechanism has been demonstrated for 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 continuously exposed to 63 mg/m^3 of a diesel-engine lubricating oil aerosol (particle sizes of 0.34 to 1.45 µm) for 12 hours a day over a period of up to 343 days. Chemical analysis of the lung and liver tissue revealed an oil content of 0.13% and 0.03%, respectively, in the exposed mice, compared with 0% in the control animals (ATSDR 1997; DECOS 2011).

Mineral oils were found to accumulate in the lungs of humans and animals after inhalation or ingestion. Once absorbed, the mineral oils are distributed preferentially in the liver and adipose tissue, slowly metabolized and eliminated via the bile with the faeces (ATSDR 1997).

The following concentrations of mineral oil saturated hydrocarbons (MOSH) were recorded (arithmetic mean and range) in tissue samples from 37 deceased persons (11 women, 26 men, aged 25 to 91, average age 67 years): mesenteric lymph nodes 232 (21–1390) mg/kg, liver 131 (14–901) mg/kg, adipose tissue 130 (17–493) mg/kg, spleen 93 (6–1400) mg/kg. The concentrations in the lungs, kidneys and heart were considerably lower at 12, 6 and 9 mg/kg, respectively, and the concentration in the brain was below the detection limit of 2 mg/kg. Higher mean concentrations were found in the tissues of the women than in those of the men. The more frequent use of cosmetics containing mineral oils by women was suggested as a possible cause. The concentrations increased with the age of the subjects. No aromatic mineral oil hydrocarbons were found. The total concentration of MOSH in the body was in the range from 0.35 to 13.3 g. The MOSH consisted of *n*-alkanes and branched and cyclic alkanes that could not be separated chromatographically. The composition of the MOSH in the lymph nodes and adipose tissue was identical. It covered the range from *n*-C16 to *n*-C35, included hydrocarbons of plant origin (*n*-C29, *n*-C31, *n*-C33), and peaked at *n*-C23 to *n*-C24. In the spleen and liver, it ranged from *n*-C18 to beyond *n*-C45, did not include hydrocarbons of plant origin, and peaked at *n*-C25 to *n*-C27. The composition of the MOSH varied from individual to individual, but the composition in the spleen and liver was very similar for any given subject. The study provided evidence that mineral oil components > C25 can accumulate in the body (Barp et al. 2014). An attempt was made to describe the alkanes in these tissues in greater detail by two-dimensional gas chromatography.

n-Alkylcyclopentanes, *n*-alkylcyclohexanes and polycyclic naphthenes were found in addition to *n*-alkanes, isoalkanes and multi-branched alkanes. The multi-branched alkanes could not be separated by two-dimensional gas chromatography. Clear signals were generated in the adipose tissue and lymph nodes, while they were markedly reduced in the liver and spleen. Evidently, the degradation of highly branched cyclic alkanes proceeds at the slowest rate in the liver, which leads to their accumulation. A comparison of the chromatograms of mineral oils and those of the tissue samples revealed that the saturated alkanes detected in the tissues were in fact from mineral oils. It remains unclear why the composition of the MOSH in the liver and spleen differs from that in the lymph nodes and adipose tissue (Biedermann et al. 2015). A possible explanation may be that a fraction of the mineral oils in the small intestine is transported to the blood via the lymph without passing through the liver (Smith et al. 1996) and is deposited in the lymph nodes and adipose tissue in a relatively unmetabolized form.

In rats, it was found that 60% of C14 hydrocarbons, 5% of C28 hydrocarbons and practically 0% of hydrocarbons > C32 are absorbed after oral administration (DECOS 2011). After ingestion, F344 rats absorbed about 3% of medium and high viscosity white mineral oils, which contain small amounts of hydrocarbons < C30. By contrast, eicosanylcyclohexane (C26), which is considered representative of the group of low viscosity white mineral oils, was eliminated with the urine in the form of acid metabolites in amounts of up to 25% depending on the dose by female SD and F344 rats given oral doses (documentation "White mineral oil, pharmaceutical" 2015).

The mineral oil with the CAS number [72623-83-7] (C > 25) has a viscosity of 550 mm^2/s at 40 °C (Dalbey et al. 2014). This means that it is highly viscous and is hardly absorbed after oral administration. The other two mineral oils that are evaluated in this documentation are even more viscous because they have a higher carbon number. They are not absorbed after oral administration. The white mineral oil with the CAS number [92062-35-6] (C > 12) is absorbed after oral administration; however, oral absorption is of little relevance for exposure at the workplace.

In several in vitro and in vivo studies with human and porcine skin, about 1% of the amount of C16 to C28 alkanes applied were shown to penetrate the skin (Nash et al. 1996).

3.2 Metabolism

The hydrocarbons of mineral oils containing longer-chain molecules are metabolized to various lipids (fatty acids or triglycerides) only to a slight extent, if at all (see above) (ATSDR 1997).

4 Effects in Humans

There are no data available for the end points single exposure, reproductive toxicity, genotoxicity and carcinogenicity.

Repeated oral (aspiration) or inhalation exposure to lipid-like products can induce exogenous lipid pneumonia in adults. In a retrospective study, 4 of 44 cases were

caused by inhalation 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).

A worker in a steel mill (former smoker) complained of a sore throat, hoarseness and dyspnoea during exertion. All symptoms, with the exception of dyspnoea, were reversible at weekends and during holiday leave. Lung biopsy revealed fibrosis and lipid pneumonia. These and similar symptoms such as coughing and bronchitis were observed in 6 other workers of the company. Gravimetric analysis of 2 samples from the workplace yielded mineral oil concentrations of 0.6 and 0.7 mg/m^3. However, there was also simultaneous exposure to a water-soluble coolant of unknown composition and kerosene. In addition, the authors pointed out the following limitations of the study: the substances used at the workplace were not analysed, which means that the effects may have been caused by a constituent of the mineral oil, the analysis of the concentration in the indoor air was not representative and a histological examination was not carried out to confirm the presence of mineral oil in intracellular and extracellular vacuoles. As these kinds of findings are often not recorded, despite the frequency of exposure, the authors assumed that in the studies that investigated this type of exposure to mineral oil, the persons were incorrectly regarded as healthy despite existing symptoms in the lungs because radiological examinations yielded normal findings and the affected workers had moved to a different workplace. Earlier studies are cited that recorded no complaints after exposure to concentrations up to 9 mg/m^3 (see below) (Cullen et al. 1981).

After occupational exposure in a steel mill to a 4% to 8% mineral oil emulsion in water for periods ranging from 9 to 18 years (n = 19), no work-related cases of lipid pneumonia, focal pneumonia, bronchitis, gastric disorders, dermatological conditions or diseases of the ears, nose and throat were reported. Radiological examination of 12 of the workers revealed an increase in linear striations in the lungs. The oil concentrations at 3 stationary points in the mill ranged from 0.78 to 9 mg/m^3. The air was collected by suction through a funnel to a washing bottle containing distilled water. The apparatus was then rinsed with ether and the water extracted by ether. A microscope was used to determine the diameter of the oil droplets, which was in the range from 0.8 to 1 µm for 70% of the droplets. The composition of the oil was about 85% of a naphthenic spindle oil with petroleum sulfonates and rosin soaps acting as emulsifiers and cresylic acid acting as a preservative. Exposure to the maximum concentration lasted for 2 hours per shift (Jones 1961). The method of analysis used in this study does not comply with today's standards, its validity is therefore unclear. For this reason, the study is not used to derive a limit value.

A large number of other more recent studies with exposure to mineral oil-based cooling lubricants are available. The findings suggest a LOEC (lowest observed effect concentration) of 0.2 mg/m^3 for mild effects on lung function (DECOS 2011). However, the adverse effects could have been caused by the additives used in these lubricants. For this reason, also these studies cannot be used to derive a limit value for pure mineral oil.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

The 4-hour LC_{50} value for rats was higher than 2460 mg/m³ for white mineral oil (Dalbey et al. 2014).

Severely 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 a concentration of 200 mg/m³ for 4 hours. The oral LD_{50} values (species not specified) were higher than 5000 mg/kg body weight, the dermal LD_{50} values for rabbits were higher than 2000 mg/kg body weight (DECOS 2011).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

After repeated inhalation of severely refined mineral oil aerosols, the lungs are the target organ in dogs, rats, mice, rabbits and hamsters (documentation "White mineral oil, pharmaceutical" 2015). After exposure of rats for 4 and 13 weeks, a NOAEC (no observed adverse effect concentration) of 50 mg/m³ and a LOAEC (lowest observed adverse effect concentration) of 210 and 150 mg/m³, respectively, were determined; the effects of exposure were increased lung weights and macrophage accumulation, thickening of the alveolar walls, epithelial hyperplasia, higher collagen content, and increased lung weights (Dalbey 2001; Dalbey et al. 1991). After exposure of mice, rabbits, hamsters, rats and dogs to mineral oil concentrations of 5 and 100 mg/m³ for 12 and 24 months, two studies (Stula and Kwon 1978; Wagner et al. 1964) yielded a NOAEC of 5 mg/m³ for rats and dogs. Mice, rabbits and hamsters are less sensitive with a NOAEC of 100 mg/m³. At these concentrations, oil deposits and (oil-laden) macrophage accumulation can be found in the lungs and oil or macrophages are observed in the hilar lymph nodes. These findings are to be considered physiological reactions that do not have an adverse effect on the lungs. Adverse effects were observed in the form of microgranulomas in the lungs of dogs and rats after exposure to a concentration of 100 mg/m³. Both studies also investigated a mouse strain with a high spontaneous incidence of lung tumours to determine whether mineral oils have a tumour promoting effect. The lung tumour incidence did not increase after 12 months of exposure to either of the two mineral oils. No effects were observed in the spleen, stomach, duodenum, adrenal glands, liver, kidneys and heart (Wagner et al. 1964). The concentrations were determined either by gravimetry with a cascade impactor and filter paper (Stula and Kwon 1978) or by an electrostatic sampler (Wagner et al. 1964). The aerosols were respirable. The values tended to be lower when the concentrations of the mineral oil aerosols in the air were analysed using filters than if they were analysed by electrostatic sampler (Volckens et al. 1999). This means that the values reported in the study of Stula and Kwon (1978) may be too low.

5.2.2 Oral administration

In subchronic studies with low viscosity white mineral oils, an accumulation of white mineral oil components and microgranulomas in the liver and mesenteric lymph nodes and histiocytosis in the mesenteric lymph nodes were observed particularly in F344 rats, but not in other species. The microgranulomas and the histiocytosis in the mesenteric lymph nodes of rats are considered to be of little relevance for humans. These effects were not observed in F344 rats after exposure to medium and high viscosity white mineral oils with a viscosity > 70 mm^2/s at 40 °C (8.97 mm^2/s at 100 °C) (documentation "White mineral oil, pharmaceutical" 2015).

No adverse effects were observed in F344 rats in 2-year studies with a medium and a high viscosity white mineral oil (70.4 mm^2/s at 40 °C = 8.97 mm^2/s at 100 °C and 100.3 mm^2/s at 40 °C = 11.3 mm^2/s at 100 °C, respectively) up to the highest dose tested of 1200 mg/kg body weight (Trimmer et al. 2004).

5.2.3 Dermal application

No histopathological changes were observed in mice, rats and rabbits in studies with in some cases lifelong dermal application of white mineral oil (BfR 2018).

In a subchronic study, a hydrotreated bright stock-based lubricating oil (petroleum), C > 25, was applied non-occlusively to the skin of 10 male and 10 female Sprague Dawley rats in a dose of 2000 mg/kg body weight and day, on 5 days a week. Ingestion was prevented by a collar. Clinico-chemical and urine parameters were determined and the weights of adrenal glands, gonads, heart, kidneys, liver, spleen and thymus were examined. A haematological examination, and histopathological examination of the intestines, duodenum, gonads, kidneys, liver, lungs, spleen, treated and untreated skin, adrenal glands, thymus, thyroid, stomach, and of macroscopic lesions were carried out. In the males, the relative kidney weights were increased by 10%, which was attributed to the reduced body weights. In the females, the relative liver weights were increased by 10%, but without a histopathological correlate. This finding was observed with several mineral oils and is thus to be considered substance-induced; other effects were not observed. The weights of the reproductive organs remained unchanged (Dalbey et al. 2014).

5.3 Local effects on skin and mucous membranes

Severely refined mineral oils cause almost no irritation of the skin and eyes of rabbits (DECOS 2011).

A comprehensive investigation of the irritant effects of mineral oils and their constituents on the skin of guinea pigs found that aliphatic compounds (*n*-paraffins, isoparaffins, monocyclic and polycyclic naphthenes) with a boiling point of 350 °C (about C21 to C23) and above no longer caused irritation of the skin. The maximum skin irritation was induced between C14 and C19. By contrast, for the respective aromatic compounds (monocyclic, bicyclic, tricyclic), skin irritation was induced up to the C24 aromatics, the fraction with the highest boiling point (Hoekstra and Phillips 1963). As severely refined mineral oils do not contain any aromatic com-

pounds and have > 25 carbon atoms, the absence of an irritant effect on the skin is consistent with the findings of this study.

5.4 Allergenic effects

5.4.1 Sensitization of the skin

The ECHA database includes two Bühler tests with undiluted mineral oils, 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 1 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 challenge treatment with a 25% preparation, but 6 of 10 and 5 of 10 animals reacted 24 and 48 hours, respectively, after repeated challenge treatment with the same concentration (ECHA 2016 a). 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, contact sensitization is not to be expected. The contact sensitizing potential of these kinds of purified paraffin oils is to be regarded as the same as that of (white) petrolatum, which likewise does not have a sensitizing potential and is therefore used as the vehicle in patch tests with humans (Schnuch et al. 2006).

5.4.2 Sensitization of the airways

There are no data available.

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 Sprague Dawley 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. The animals were then mated for 10 days and the females were kept up to day 21 post partum without further exposure to the substance. 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 which white mineral oil in a dose of 1 ml/kg body weight and day (about 850 mg/kg body weight) was applied to the skin of 10 male and 10 female Sprague Dawley rats per group, no effects on reproduction were observed in comparison with the findings in sham-treated control animals. In deviation from the test guideline, the male animals were treated for 8 instead of 4 weeks and 7 organs were weighed in addition to the reproductive organs (Schreiner et al. 1997).

In a 1-generation study carried out using a procedure similar to OECD Test Guideline 415, 20 male and 20 female Sprague Dawley rats were exposed to white mineral oil doses of 0, 125, 500 or 2000 mg/kg body weight and day by open dermal application on 5 days a week (10 weeks before mating, during a 3-week mating period, during gestation and until weaning of the pups). No adverse effects on reproduction were found. Skin irritation was induced in all treated male animals (Dalbey et al. 2014; ECHA 2016 a).

In a 13-week study, a hydrotreated bright stock-based lubricating oil (petroleum), C > 25, was applied non-occlusively to the skin of 10 male and 10 female Sprague Dawley rats in doses of 0 or 2000 mg/kg body weight and day, on 5 days a week. The weights and histopathology of the reproductive organs remained unchanged in comparison with the findings in the control animals that had been treated with water (Dalbey et al. 2014).

In 13-week studies, 2 white mineral oils were applied non-occlusively to the skin of 10 male and 10 female Sprague Dawley rats in a dose of 1300 mg/kg body weight and day, on 5 days a week. The weights and histopathology of the reproductive organs remained unchanged in comparison with the findings in the sham-treated control animals (Dalbey et al. 2014).

5.5.2 Developmental toxicity

In a developmental toxicity study carried out using a procedure similar to OECD Test Guideline 414 (only 1 concentration tested), 20 Sprague Dawley rats were whole-body exposed to a white mineral oil aerosol (CAS number [8042-47-5]) at a concentration of 1000 mg/m^3 (mass median aerodynamic diameter of 1.2 µm) for 6 hours a day, from gestation days 6 to 19. Developmental or maternal toxicity were not observed (Dalbey et al. 2014; ECHA 2016 a).

In a developmental toxicity study carried out using a procedure similar to OECD Test Guideline 414 (only 1 dose over the limit dose tested), 20 Sprague Dawley rats were given daily gavage doses of 5000 mg/kg body weight of the same white mineral oil as in the above-described study from gestation days 6 to 19. Developmental or maternal toxicity were not observed (Dalbey et al. 2014; ECHA 2016 a).

White mineral oil was used as a vehicle control in two studies in which groups of 49 and 25 Sprague Dawley 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 3 of 25 litters, respectively. No specific patterns of malformation were recognizable (McKee et al. 1987 b) and the malformations were therefore not regarded as substance-induced.

In a developmental toxicity study carried out using a procedure similar to OECD Test Guideline 414 (only 1 dose over the limit dose tested), daily doses of white mineral oil of 2000 mg/kg body weight were applied to the skin of 20 Sprague Dawley rats from gestation days 6 to 19. Developmental or maternal toxicity were not observed (Dalbey et al. 2014; ECHA 2016 a).

5.6 Genotoxicity

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

5.7 Carcinogenicity

In long-term studies with severely refined mineral oils in rats and dogs, the tumour incidence was not increased after exposure to the highest concentration tested of 100 mg/m^3, and a promotion of lung tumours was not observed in a sensitive mouse strain after 12-month exposure to 100 mg/m^3 (Stula and Kwon 1978; Wagner et al. 1964).

Tumours were not found in mice and rats after oral, dermal or subcutaneous exposure to refined mineral oils (DECOS 2011).

Skin painting studies in CF1 and C3H mice were carried out with 67 mineral oils with a DMSO-extractable content of less than 3%. Of these, 3 were carcinogenic (skin tumours were induced in more than 4% of the animals), and 2 of these induced a tumour incidence of 5%. Of 37 tested mineral oils with a DMSO-extractable content greater than 3%, all but 3 were carcinogenic. The benzo(a)pyrene content did not correlate well with either the percentage of DMSO-extractable substances or with the tumour incidence. On the basis of this study, a DMSO-extractable content of 3% has been established as the cut-off value for classification as a carcinogen (CONCAWE 1994).

6 Manifesto (MAK value/classification)

The target organ in animal studies was the lungs; the dog and rat were the most sensitive species.

MAK value. There are no data in humans available that can be used to derive a MAK value.

The lungs are the target organ in dogs, rats, mice, rabbits and hamsters after repeated inhalation of respirable aerosols of severely refined mineral oils. A NOAEC of 50 mg/m^3 was reported after exposure of rats for 13 weeks, and a NOAEC of 5 mg/m^3 was determined after exposure of rats and dogs for 12 and 24 months, based on microgranulomas in the lungs found at 100 mg/m^3. The margin between the NOAEC of 5 mg/m^3 from the long-term studies in rats and dogs and the LOAEC of 100 mg/m^3 is sufficiently large, also taking into consideration the NOAEC of 50 mg/m^3 after 13-week exposure of rats and the increased respiratory volume. As no great interindividual variation and no differences in metabolism are to be expected as regards pulmonary overloading (the critical effect), and as elimination takes place via the macrophages into the lymph, the MAK value for pharmaceutical white mineral oil of 5 mg/m^3 R has likewise been established for severely refined mineral oils.

The same value is obtained if an alternative approach is used to derive the MAK value that is based on the NOAEC of the 13-week study and takes into consideration the possible decrease of the NOAEC after long-term exposure (1:2), the increased respiratory volume (1:2), the extrapolation of the data from animal studies to humans (1:2) and the preferred value approach.

Peak limitation. As the effects on the lungs are cumulative and occur late, severely refined mineral oils have been classified in Peak Limitation Category II. In analogy to polyalphaolefins (documentation "Polyalphaolefine" 2011, available in German only) and pharmaceutical white mineral oil (documentation "White mineral oil, pharmaceutical" 2015), an excursion factor of 4 has been established for the limitation of exposure peaks.

Prenatal toxicity. In rats, neither inhalation exposure to a white mineral oil concentration of 1000 mg/m³ 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 for the rat (1:4), oral absorption of 5% (experimental determination for C28 hydrocarbons), the body weight (70 kg) and respiratory volume (10 m³) of the person and the assumed 100% absorption by inhalation. The concentration calculated from this is 438 mg/m³. Taking into consideration the increased respiratory volume (1:2), the 100-fold margin between the MAK value of 5 mg/m³ R and the NOAEC for inhalation exposure and the 88-fold margin between the MAK value and the calculated concentration in air are sufficiently large to classify severely refined mineral oils in Pregnancy Risk Group C.

Carcinogenicity and germ cell mutagenicity. Severely refined mineral oils are neither genotoxic nor carcinogenic. Therefore, the substances are not classified in one of the categories for either carcinogens or germ cell mutagens.

Absorption through the skin. In vitro, the maximum amount of C16 and C25 aliphatics absorbed through the skin of humans and pigs was 1%. It may therefore be assumed that absorption through the skin is very low after epicutaneous application of mineral oil and does not contribute to systemic toxicity. For this reason, severely refined mineral oils are not designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are no clinical findings or findings from animal studies for sensitization. The data available for other saturated hydrocarbons (in particular paraffin oil and petrolatum) indicate that these substances do not have a sensitizing effect on the skin or airways. Severely refined mineral oils are therefore not designated with "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

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