1144

Distillates (petroleum), hydrotreated light

MAK Value Documentation

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the maximum concentration at the workplace (MAK value) of hydrotreated light distillates (petroleum) [64742-47-8] of 20 ml/m³, considering all toxicological endpoints. Available publications and unpublished study reports are described in detail. The critical effect of hydrotreated light distillates (petroleum) (C9–C16) vapours is presumably CNS-depression as is the case with other hydrocarbon mixtures like White Spirit. For the aerosol phase lung toxicity is assumed to be the critical effect. The Commission increased the MAK value for the vapour phase to 50 ml/m³ in analogy to hydrotreated heavy naphtha (petroleum) (C6–C13) for which behavioural studies with White Spirit (C9–C12) in volunteers were used to derive the MAK value. White Spirit can be viewed as representative for hydrotreated light distillates (petroleum) because their C13–C16 components have low vapour pressure and do not contribute much to the concentration in the vapour phase. On the other hand, the aerosol phase comprises mostly these components and they are expected to be deposited as aerosol in the lung. A MAK value of 5 mg/m³ for the respirable fraction in analogy to White Oil is set. As systemic effects are critical, the assignment to Peak Limitation Category II is retained. The excursion factor of 2 for the vapour is confirmed and an excursion factor of 4 for the aerosol is set in analogy to White Oil. The assignment to Pregnancy Risk Group C is confirmed, as there is no reason to fear damage to the embryo or foetus when the MAK value is observed. Hydrotreated light distillates are not genotoxic. After chronic epicutaneous application of high doses of kerosenes malign skin tumours developed in mice. However, since the relevance of these tumours for humans in this model is not clear, the assignment to Carcinogen Category 3B is retained. Skin contact does not contribute to systemic toxicity and sensitization is not expected.

Keywords

petroleum distillates; hydrotreated distillates; light distillates; mechanism of action; (sub)acute toxicity; (sub) chronic toxicity; 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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[64742-47-8]

Supplement 2016

MAK value (2015)	**50 ml/m³ ≙ 350 mg/m³ (vapour)** **5 mg/m³ R (respirable fraction) (aerosol)**
Peak limitation (2015)	**Category II, excursion factor 2 (vapour)** **Category II, excursion factor 4 (aerosol)**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity (2011)	**Category 3B**
Prenatal toxicity (2011)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**

Documentation was published for hydrotreated light distillates (petroleum) in 2012 (documentation "Distillates (petroleum), hydrotreated light" 2012).

This supplement is a re-evaluation following the publication of new studies: a 13-week study with a **C10–C12** isoparaffin product (boiling point: 170°C to 187°C) (Carrillo et al. 2013; Shell 1980) and other studies with C8–C15 aliphatics that the authors considered to be representative of **C9–C14** dearomatized aliphatic products (Carrillo et al. 2013), a product group that includes hydrotreated light distillates (petroleum).

In addition, registration data for CAS number 64742-47-8 have become publicly available on the ECHA website (ECHA 2014).

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The Commission evaluated the following petroleum products:

1. Naphtha (petroleum), hydrotreated heavy; MAK value: 50 ml/m³ = 300 mg/m³ (documentation "Naphtha (petroleum), hydrotreated heavy" 2010);
   defined as hydrocarbons, paraffinic and naphthenic, **C6–C13**, distillation range: 65°C to 230°C, free of aromatics, CAS number: 64742-48-9. The evaluation focused primarily on studies with white spirit (with and without aromatics). The MAK value was derived from human data (CNS effects). According to the SCOEL, white spirit type 3 (dearomatized white spirit) corresponds to this CAS number, but only makes up a fraction of this because the primary components of white spirit type 3 are C9–C11 hydrocarbons.
   The data registered in the ECHA database for CAS number 64742-48-9, however, are based almost exclusively on studies with unleaded petrol (CAS numbers 86290-81-5 and 8006-61-9) with a distillation range of 30°C to 260°C.
2. Distillates (petroleum), hydrotreated light; MAK value: 20 ml/m³ = 140 mg/m³ (documentation "Distillates (petroleum), hydrotreated light" 2012);
   defined as hydrocarbons with carbon numbers predominantly in the range of **C9–C16**, distillation range: 150°C to 290°C, CAS number: 64742-47-8. This evaluation focused primarily on studies with hydrodesulfurized and deodorized kerosene.

The data registered in the ECHA database for this CAS number are based almost exclusively on studies with kerosene, especially jet fuel JP-8 (C9–C16, but with 20% aromatics and additives), hydrodesulfurized kerosene (CAS number: 64742-81-0) or low aromatic white spirit. Therefore, this evaluation also includes studies with jet fuel JP-8 or other aviation kerosenes for various end points.

CAS number 64742-47-8 describes a hydrotreated petroleum fraction. Hydrotreatment is used to remove organic sulfur from the petroleum fraction. There is no information about the residual amounts of aromatics or olefins, which are reduced to naphthenic or paraffinic compounds by hydrotreatment. This means that aromatics and olefins may still be present in differing amounts. In IARC (1989), this CAS number refers to the hydrotreated kerosene process stream. Non-hydrotreated kerosene is straight-run kerosene with CAS number 8008-20-6 and the same carbon number and distillation range. Table 1 describes various petroleum fractions that are relevant to the evaluation of hydrotreated light distillates (petroleum).

This supplement also contains the main findings and descriptions of studies relevant to this evaluation that were included in the 2012 documentation (documentation "Distillates (petroleum), hydrotreated light" 2012).

"Hydrotreated light distillates (petroleum)" are a complex mixture of hydrocarbons obtained by treating a petroleum fraction with hydrogen in the presence of a catalyst. This mixture consists of hydrocarbons with carbon numbers predominantly in the range of C9 to C16 and boiling points in the range of 150°C to 290°C; it is a by-product in petroleum refining. Annual production is more than 1 million tons (documentation "Distillates (petroleum), hydrotreated light" 2012).

There are no toxicological studies available with a mixture that corresponds exactly to the definition given by CAS number 64742-47-8. Studies with mixtures with

Table 1 Distillation range and C number of various petroleum fractions and the level of aromatics they contain

Fraction	Distillation range	C number	Aromatics
kerosene, straight run 8008-20-6	150–290	9–16	no data
kerosene, hydrotreated 64742-47-8	150–290	9–16	no data
kerosene, hydrodesulfurized 64742-81-0	180–280 84–290	9–16	around 20% 17%
deodorized kerosene	207–270		4%
jet fuels/JP (= kerosene + additive)			
jet fuel A	180–271 163–283		around 20% around 22%
jet fuel JP-5	176–260		around 16%
jet fuel JP-8	90%: 205–308	8–15	around 14%–18%
middle distillate	205–345 177–370	11–20	no data
mineral oil	> 300	> 15	no data
white mineral oil	218–800	15–50	0%

narrower distillation ranges are available, for example from 205°C to 237°C (documentation "Distillates (petroleum), hydrotreated light" 2012).

Because of their structural similarity, these hydrocarbons are presumably all oxidized in the organism at the alkyl chain or alkyl ring to form alcohols, aldehydes and acids or ketones. Therefore, the toxicity of the compounds of this group is expected to be qualitatively similar to that of the individual representatives that were investigated; this included CNS effects, liver tumours in the case of branched compounds, and nephrotoxicity. The Commission evaluated "naphtha (petroleum), hydrotreated heavy" in 2010 (documentation "Naphtha (petroleum), hydrotreated heavy" 2010). These substances consist of aromatic-free C6–C13 hydrocarbons with a distillation range of 65°C to 230°C. "Distillates (petroleum), hydrotreated light" are a similar mixture, but with higher boiling points. For this reason, the findings from "naphtha (petroleum), hydrotreated heavy" can be used as a reference for the assessment of the proportion of components with lower boiling points in "distillates (petroleum), hydrotreated light". Thus, this evaluation focuses primarily on studies with aromatic-free petroleum fractions in most cases and with boiling points in a higher range (> 180°C) (documentation "Distillates (petroleum), hydrotreated light" 2012).

Studies of genotoxicity in vivo or carcinogenicity are not available. However, these end points were investigated with various kerosenes, for example hydrodesulfurized kerosene (distillation range: 183°C to 279°C; contains 49% paraffins, 31.4% cycloparaffins, 0.76% olefins and about 19% aromatics, 11.4% of which are

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alkylbenzenes and 1.55% naphthalene derivatives; mean molar mass: 173 g/mol) (documentation "Distillates (petroleum), hydrotreated light" 2012). The evaluation includes these studies because the distillation ranges and carbon numbers are similar. An aromatic level of 19% should not have any major influence on acute toxicity (see documentation "Naphtha (petroleum), hydrotreated heavy" 2010) or carcinogenicity. Hydrodesulfurized kerosene did not contain relevant quantities of known carcinogens such as aromatic hydrocarbons with 4 to 6 rings. However, the amount of benzo[*a*]pyrene in petroleum middle distillates with distillation ranges of 177°C to 370°C was below 1 mg/kg. As a result of the lower maximum boiling point of hydrodesulfurized kerosene, it is expected to have an even lower PAH (polycyclic aromatic hydrocarbon) level. In addition, studies with deodorized kerosene (distillation range: 207°C to 272°C, 55.2% aliphatics, 40.9% alicyclics, 3.9% aromatics), petroleum middle distillates (distillation range: 163°C to 315°C or up to 370°C), jet fuel JP-8 and aromatic-free products are included in the evaluation if their maximum boiling points or maximum chain lengths are similar to those of "hydrotreated light distillates (petroleum)" (documentation "Distillates (petroleum), hydrotreated light" 2012).

As these are mixtures of substances, concentrations can be given in ml/m^3 only if the mean molar mass is known. To simplify matters, where the studies do not give an explicit conversion, a molar mass of 170 g/mol is assumed for converting mg/m^3 into ml/m^3 and vice versa; this corresponds approximately to a chain length of C12 (documentation "Distillates (petroleum), hydrotreated light" 2012).

This re-evaluation differentiates between the vapour fraction and aerosol fraction. Jet fuel JP-8 contains more shorter-chain hydrocarbons in the vapour phase and more longer-chain hydrocarbons in the aerosol phase, but the fraction of C13–C17 compounds in the aerosol is at the most twice as high as in the liquid. The limit of depletion/accumulation is about C12 (JP-8; Gregg et al. 2007). The concentration is determined based on the sum of the CH compounds from C9 to C16; the vapour saturation concentration of n-C14 is only 15 ml/m^3 and the vapour saturation concentrations of n-C15 and n-C16 are even lower. However, the saturation concentrations of C9, C10, C11, C12 and C13 are far higher. Thus, at a given total concentration of C9 to C16, there is only a very low fraction of C14 to C16 in the vapour phase. Therefore, studies with white spirit (C9–C13) can also be used to evaluate the toxicity of the vapour phase of petroleum distillates.

Toxic Effects and Mode of Action

The tested petroleum distillates are of low acute toxicity. Single applications caused mild irritation to the rabbit skin, and repeated applications caused skin irritation in mice. The products induced mild irritation to the eyes and were not sensitizing to the skin or genotoxic.

In a 13-week study in rats with gavage doses of a product free of aromatics, alpha2u nephropathy not relevant to humans was observed in male rats but not in

females at the lowest dose tested of 100 mg/kg body weight and day and above. The relative liver weights and the absolute and relative kidney weights were increased in males and females at 500 mg/kg body weight and above, and changes in clinico-chemical parameters were found.

In a 13-week inhalation study with a C10–C12 isoparaffin product in rats, relative liver weights were increased by 40% at 1444 ml/m^3, and lethargy was observed in the animals after exposure. After continuous 13-week exposure of rats to jet fuel JP-8, no adverse effects were observed at 1000 mg/m^3 (about 140 ml/m^3).

No toxic effects on reproduction were observed up to the highest dose tested that was not toxic to the parents. In a long-term study, dermal application of petroleum distillates such as **hydrodesulfurized kerosene** with a distillation range similar to that of "hydrotreated light distillates (petroleum)" caused benign and malignant tumours on the skin of mice and promoted skin tumours after initiation in short-term studies. Further studies with various kinds of kerosenes confirmed these findings.

Effects in Humans

Deodorized kerosene vapour (distillation range: 207°C to 272°C, 55.2% aliphatics, 40.9% alicyclics, 3.9% aromatics) did not cause sensory irritation to the eyes, nose or throat in 6 volunteers after exposure to a concentration of 20 ml/m^3 (140 mg/m^3) for 15 minutes. The odour threshold was about 0.09 ml/m^3. According to the authors, 20 ml/m^3 corresponded to the vapour saturation concentration (Carpenter et al. 1976; documentation "Distillates (petroleum), hydrotreated light" 2012).

Thus, the NOAEC (no observed adverse effect concentration) was 20 ml/m^3 for humans. Higher concentrations were not tested although higher vapour concentrations with kerosene could have been generated because there are studies available in rats with jet fuel JP-8 vapour in concentrations up to 140 ml/m^3 (Mattie et al. 1991) and measured values from tanks in which jet fuel JP-8 was stored where the sum of n-nonane, n-decane, n-undecane and n-dodecane, the main components of JP-8, was about 100 ml/m^3 (Pleil et al. 2000).

A study with low-aromatic white spirit and white spirit containing aromatics (distillation range: about 140°C to 200°C in both cases, C9–C12) did not reveal relevant toxic effects on behaviour in subjects up to 300 mg/m^3 (50 ml/m^3) after exposure for 4 hours (Juran et al. 2014).

Animal Experiments and in vitro Studies

Subacute, subchronic and chronic toxicity

Inhalation

In a 28-day study with nose-only exposure to additive-free jet fuel kerosene concentrations of 0, 500, 1000 or 2000 mg/m^3 for 6 hours a day, on 7 days a week, no toxic

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effects on the humoral, cell-mediated and innate immune functions were detected in female B6C3F1 mice or Crl:CD rats. The lowest concentration was in vapour form, while the two higher concentrations were mixtures of vapour and aerosol (88% and 75% vapour, respectively) (White et al. 2013).

In a 13-week study with groups of 19 male albino rats exposed in whole-body chambers for 6 hours a day on 5 days a week to deodorized kerosene, which was introduced into the exposure chamber as an aerosol, no effects were observed on the blood count, clinico-chemical and urine parameters or organ weights compared with the values for the controls at vapour concentrations of 0, 20, 48 or 100 mg/m³ (0, 3, 7, 14 ml/m³). There were no histopathological abnormalities in the lungs, liver, kidneys, heart, spleen, adrenal glands, thyroid, trachea or oesophagus. Groups of 4 male beagle dogs per concentration group were exposed and examined in the same way. No adverse effects were found in this study either (Carpenter et al. 1976; documentation "Distillates (petroleum), hydrotreated light" 2012). The range of 14 to 20 ml/m³ corresponds approximately to the vapour saturation concentration. The given concentrations may have been too low because the nominal concentrations were 4 to 5 times higher than those determined. It is thus possible that the animals were also exposed to an aerosol. The NOAEC was 14 ml/m³ or higher (documentation "Distillates (petroleum), hydrotreated light" 2012).

In a study from 1980 with an aromatic-free product (C10–C12 isoparaffins, 170°C to 187°C), 18 male and 18 female Wistar rats (10 to 13 weeks old) per group were exposed to concentrations of 0, 359, 737 or 1444 ml/m³ in whole-body exposure chambers on 5 days a week, for 6 hours a day, for 13 weeks (see Table 2; Carrillo et al. 2013; Shell 1980). During the study, the general state of health and behaviour were observed and body weight gains were determined. At the end of exposure, haematological, clinico-chemical, gross-pathological and histopathological examinations were carried out (29 organs were examined via gross pathology, 22 of these via histopathology including the nose but without the larynx) and the weights of 6 organs were determined. Increased absolute and relative liver weights were the most sensitive end points in males at the lowest concentration and above, but no histological or clinico-chemical (ASAT = aspartate aminotransferase/ALAT = alanine aminotransferase) effects were detected. The absolute weights were increased by less than 10% at 359 ml/m³, by 14% at 737 ml/m³ and by about 40% at 1444 ml/m³.

At 359 ml/m³ and above, body weight gains were slightly reduced in the females independent of the concentration, and ASAT and ALAT activities were reduced (no toxic effects; according to the authors, the control levels were lower than the historical control values). In the males, increased absolute and relative liver and kidney weights (probably as a result of alpha2u globulin), slight anaemia (erythrocytes: –3%; PCV: reduced; haemoglobin: reduced) and signs of alpha2u-globulin nephropathy were observed, but alpha2u globulin itself was not examined.

At 737 ml/m³ and above, the chloride concentration was increased in the blood independent of the concentration, and the percentage of eosinophils was increased in the blood of the male animals, while in the females the absolute and relative liver weights were increased.

At 1444 ml/m^3, in male animals the body weight gains were transiently reduced, the potassium concentration, alkaline phosphatase activity and the albumin and kaolin-cephalin concentrations were increased, the leukocyte/lymphocyte counts were reduced, the percentage of neutrophils was increased, the leukocyte count was reduced, and the heart and spleen weights and the incidence of chronic inflammatory infiltrates in the lungs were increased (this was relativized by the authors as a normal occurrence in this strain); in females the protein and albumin concentrations and the percentage of leukocytes were increased, the percentage of neutrophils was reduced and the absolute and relative kidney weights were increased. Lethargy was observed in both sexes after exposure (evidence of an acute CNS effect).

The authors of the study interpreted the results as follows: The mixture induced mild anaemia and slight degenerative changes in the kidneys of the males in all concentration groups. The increased liver weight was an adaptive effect. A NOAEC was not given in the study report. In the study of Carrillo et al. (2013), the highest concentration of 1444 ml/m^3 was reported as the NOAEC; the lethargy observed in this concentration group was thus not regarded as adverse or not taken into account.

Evaluation of the Commission: the **anaemia** was only very mild, there was no clear dependence on the concentration and it occurred only in the males. However, mild anaemia in male rats was found also after exposure to other aliphatic solvents (Carrillo et al. 2013). The authors gave the normal variations in blood parameters as a possible explanation. They pointed out that these changes were consistent with those described as anaemia of chronic disease. Such changes were often observed in studies with high doses and are not toxicologically relevant (Car et al. 2006). At 1100 mg/m^3 and above, the study using Stoddard Solvent IIC (C10–C14, level of aromatics: maximum of 1%; NTP 2004) revealed mild anaemia in male F344 rats after 3 months, but not in females or in male and female B6C3F1 mice. Stoddard Solvent IIC also caused alpha2u nephropathy only in male F344 rats. Therefore, anaemia is assumed to be a secondary effect. The NTP considered the findings of anaemia to be toxicologically irrelevant (NTP 2004). In the high concentration group, reduced **leukocyte counts** were observed only in male rats. Leukocyte numbers vary considerably among rat strains (Car et al. 2006). Furthermore, the initial age of the animals is of importance for evaluating this effect because leukocyte counts decrease in the course of a rat's life (NTP 2004). Most other aliphatic solvent mixtures had no effects on the leukocyte count. **Lethargy** occurred in the high concentration group after exposure. This is an adverse effect on the CNS. The authors considered the increased **liver weights** to be an adaptive effect because no histological findings were obtained in the liver and ASAT and ALAT activities were not increased. This effect may have been caused by the induction of xenobiotic-metabolizing enzymes, but this was not investigated. The Commission considers a 40% increase in the absolute liver weights of the high concentration group by enzyme induction to be adverse because it may interfere with metabolic processes. However, the middle concentration that induced a 13% increase may be regarded as the NOAEC. There was a concentration-dependent increase in the incidences of **inflammatory infiltrates**

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Table 2 Main findings of the 13-week study with a product free of aromatics (C10–C12 isoparaffins, 170°C–187°C) (Shell 1980)

Parameter		Concentration			
		controls	2529 mg/m³ (359 ml/m³)	5200 mg/m³ (737 ml/m³)	10 186 mg/m³ (1444 ml/m³)
Hb (g/dl)	♂	15.0	14.6*	14.3**	14.4**
	♀	14.6	14.3	14.5	14.1
PCV (%)	♂	41	40.0**	39.0**	39.0**
	♀	40	39	39	39
RBC (10^6/mm³)	♂	7.79	7.57*	7.46**	7.46**
	♀	7.07	7.00	7.05	6.93
WBC (10^3/mm³)	♂	4.5	4.6	4.0	3.6**
	♀	2.8	2.9	2.8	3.0
MCHC (g/dl)	♂	36.1	36.4	36.2	36.6*
	♀	36.3	36.1	36.4	36.3
KCCT (sec)	♂	24.3	25.0	26.5	26.8*
	♀	23.2	22.4	21.3	22.7
AP (IU)	♂	86	87	92	100.0*
	♀	56	55	50	54
ALAT (IU)	♂	29	30	34	36
	♀	27	21.0*	21.0**	19.0**
ASAT (IU)	♂	49	46	46	47
	♀	54	43.0**	43.0**	37.0**
terminal body weight (g)	♂	498	507	501	481 (–3.5%)
	♀	294	285	289	286
absolute liver weight adjusted for terminal body weight	♂	15.4	16.59** (+7%)	17.40** (+13%)	21.00** (+36%)
	♀	8.92	9.29 (+4%)	10.09** (+13%)	12.67** (+42%)
absolute kidney weight adjusted for terminal body weight	♂	2.77	3.33** (+2%)	3.45** (+25%)	3.83** (+38%)
	♀	1.78	1.87 (+5%)	1.88 (+6%)	2.06** (+16%)
chronic inflammatory infiltrates in the lungs	♂	5/18	not examined	7/18	14/18
	♀	12/18	not examined	8/18	12/18

*$p < 0.05$; **$p < 0.01$; ALAT: alanine aminotransferase; AP: alkaline phosphatase; ASAT: aspartate aminotransferase; Hb: haemoglobin; KCCT: kaolin-cephalin coagulation time; MCHC: mean corpuscular haemoglobin concentration; PCV: (packed cell volume) haematocrit; RBC: (red blood cells) erythrocyte count; WBC: (white blood cells) leukocyte count

in the lungs of the males. The authors stated that this finding was often observed in the rats from the test laboratory and that the incidence was just as high in the control animals. However, no data were reported. The absolute **kidney weights** of the female rats were increased in the high concentration group without histological findings. The kidney findings obtained in males were caused by alpha2u nephrotoxicity; they are thus not relevant to humans.

In the high concentration group, various effects were found that the Commission regarded as substance-induced and adverse; therefore, 1444 ml/m³ is regarded as the LOAEC (lowest observed adverse effect concentration) and 759 ml/m³ as the NOAEC.

The NOAEC for jet fuel JP-8 **vapour** was 1000 mg/m³ (140 ml/m³) after continuous whole-body exposure of 15 F344 rats to 0, 500 or 1000 mg/m³ for 13 weeks. Another 10 animals per sex and group were examined 2 and 9 months after exposure, and another 46 to 50 animals per sex and group were examined 21 months after exposure. Substance-induced effects on the lungs were not observed using either a light microscope or an electron microscope, but the lung function was not examined. Body weight gains were significantly reduced only in the males (about 8% in the group that received 1000 mg/m³), which persisted up to the end of the study, and increased relative kidney weights and histopathological kidney findings were observed in the males that are consistent with alpha2u nephropathy. An increased incidence of urothelial hyperplasia was observed only in males after 2 years (100% after 2 years in the group that received 1000 mg/m³) and might thus likewise have resulted from alpha2u nephropathy. In C57BL/6 mice that were exposed in the same way, no changes in body weights, effects on the kidneys or any other effects related to exposure were found (Mattie et al. 1991).

Studies with aerosol

A working group carried out several studies with aerosolized jet fuel JP-8:

Evidence of lung effects in F344 rats were found after nose-only exposure to jet fuel JP-8 **aerosol** for 1 hour at a level of 500 mg/m³ for a period of 7 or 28 days. Compared with the findings in control animals, pulmonary resistance was increased, the concentration of substance P in the bronchoalveolar lavage fluid (BALF) was reduced, body weight gains were reduced and alveolar clearance was increased. Examination of the lungs with a light microscope did not reveal any adverse findings. A NOAEC was not obtained (Pfaff et al. 1995).

In another study, 6 groups of 9 to 27 F344 rats were exposed nose-only to jet fuel JP-8 **aerosol** concentrations of about 500 or 1000 mg/m³ for 1 hour a day, for 7, 28 or 56 days. Compared with the findings in the respective control animals, the concentration of substance P in the BALF was reduced depending on the concentration and duration, whereas that of the neutral endopeptidase was increased. The authors assumed that substance P was degraded by endopeptidase released from damaged pulmonary epithelial cells. However, it should be pointed out that the endopeptidase concentration was not increased in the low concentration group in spite of a marked reduction in the substance P concentration; therefore, a relationship be-

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tween the two markers seems questionable. Lung damage that was visible histopathologically and by electron microscope was observed in all exposed animals. Pulmonary congestion and haemorrhages were observed in the high concentration group, and focal accumulation of inflammatory cells was found in both concentration groups after 28 days (Pfaff et al. 1996).

Male C57BL/6 mice were exposed nose-only to jet fuel JP-8 concentrations of 45, 267 or 406 mg/m³ for 1 hour a day, for 7 days. The aerosol fraction was about 5% to 15%. The dynamic lung compliance was reduced in mice that were exposed to the high concentration. At 45 and 406 mg/m³, the vacuole volume density of lamellar bodies was increased, which is indicative of increased surfactant production. In addition, detachment of the epithelial cells of the airways was observed that was not dependent on the concentration (Herrin et al. 2006).

Male C57BL/6 mice were exposed to jet fuel JP-8 or a new synthetic fuel S8 (aromatic-free C7–C18, alkane-rich) in concentrations of 53 mg/m³ for 1 hour a day, for 7 days. The aerosol fraction was about 5% to 15%. S8 increased the expiratory lung resistance and JP-8 increased both the expiratory and inspiratory lung resistance compared with control values. It was shown using an electron microscope that the bronchioles were the target tissue of S8 and the alveoli and terminal bronchioles were the target tissue of JP-8. JP-8 increased the vacuole volume density of lamellar bodies in alveolar type II epithelial cells. In bronchiolar Clara cells, the vacuole volume density of secretory granules was decreased after exposure to both substances (Wong et al. 2008).

In another study, male C57BL/6 mice were exposed nose-only to synthetic jet fuel S8 for 1 hour a day, for 7 days, in concentrations of 93, 352 or 616 mg/m³. The aerosol fraction was 10% to 15%. At 352 mg/m³, the expiratory lung resistance and lung compliance were reduced, but not in a concentration-dependent manner. At 352 mg/m³ and above, the vacuole volume density of lamellar bodies was increased and blebs were observed in Clara cells (Wong et al. 2009).

Conclusions

For kerosene vapour (jet fuel JP-8), the highest concentration of 140 ml/m³ after continuous exposure for 13 weeks was the NOAEC in rats. After exposure to kerosene aerosol (jet fuel JP-8), effects on the lungs of mice were observed by electron microscope at 50 mg/m³ and above even when the animals were exposed only for 1 hour per day. Some of these effects were not concentration-dependent, and it is difficult to evaluate whether they are to be regarded as adverse. As they were not found after exposure to far higher concentrations of JP-8 vapour, the effects are attributed to the aerosol. However, it is not possible to establish a NOAEC because the effects were observed only after short-term exposure, it is unclear whether they are to be regarded as adverse, the findings were not consistent and they have not been confirmed by other research groups.

Oral administration

A 13-week study according to OECD Test Guideline 409 was carried out in SD rats using a product free of aromatics with a distillation range of 205°C to 237°C. The animals were given gavage doses of 0, 100, 500 or 1000 mg/kg body weight and day on 5 days a week. Alpha2u nephropathy was found in all exposed male animals. At 500 mg/kg body weight and above, changes in the concentrations of glucose, urea nitrogen and cholesterol and in the alanine aminotransferase and aspartate aminotransferase activities in the serum (no other details) were observed. In the males, the relative liver weights and the absolute and relative kidney weights were increased at 500 mg/kg body weight and day and above. In the females, the relative liver weights were increased and hepatocellular hypertrophy occurred. At 1000 mg/kg body weight and day, the absolute liver weights were increased in the females, and hepatocellular hypertrophy was found in the males. All findings were reversible after 4 weeks. The increased kidney weights were probably associated with the accumulation of alpha2u globulin, which is not relevant to humans. The increased liver weights were presumably the result of the induction of xenobiotic-metabolizing enzymes. The NOAEL (no observed adverse effect level) for this effect was 100 mg/kg body weight and day (documentation "Distillates (petroleum), hydrotreated light" 2012).

Reproductive and developmental toxicity

Fertility

Undiluted jet fuel JP-8 was used in a study of reproductive toxicity with groups of at least 20 Sprague Dawley rats per sex. In the first part of the study, the males were given gavage doses of 0 (1 ml distilled water), 750, 1500 or 3000 mg/kg body weight and day for 70 to 90 days and were mated with untreated females. Treatment included cohabitation. In the second part of the study, the females were exposed to gavage doses of 0 (1 ml distilled water), 375, 750 or 1500 mg/kg body weight and day for 90 days before mating, during mating and throughout gestation and lactation (21 weeks in total). The females were mated with untreated males. On postnatal day 5, the litters were standardized to 4 male and 4 female offspring per litter. Although behavioural tests were carried out, these data were not included in the study report. Mortality and clinical symptoms were not observed. Haematological and clinico-chemical parameters were examined and urinalysis was performed only in the females; no abnormalities were detected. The concentration-dependent reduction in body weights in the males (no other details) was probably caused by nephropathy, which is typical for male rats treated with hydrocarbons. At 750 mg/kg body weight and day and above, the absolute and relative liver weights of the females were reduced without any histopathological correlate and hyperplasia was found in the stomach. At 1500 mg/kg body weight and day, reduced body weights and perianal dermatitis were observed in the females. The males were not examined histopathologically because nephropathy was determined in earlier studies.

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Treatment-related effects on reproductive or sperm parameters were not detected in the males, nor were any effects on reproduction, gestation or litter size observed in the females. The body weights of the offspring were reduced on postnatal day 4 at 750 mg/kg body weight and day and above and from postnatal days 4 to 21 at 1500 mg/kg body weight and day. On postnatal day 90, the body weights returned to normal. The NOAEL and LOAEL (lowest observed adverse effect level) for systemic effects were 750 and 1500 mg/kg body weight and day, respectively, based on the reduced body weights in the dams and offspring. The LOAEL for effects on the adult male animals was 750 mg/kg body weight and day, based on the changes in clinico-chemical parameters, body weights, organ weights and perianal irritation (no other details). The interpretation of the systemic effects in males was complicated by the nephropathy that is specific to male rats and typical of hydrocarbon fuels such as jet fuel JP-4 and jet fuel JP-8. The highest doses of 3000 mg/kg body weight and day for males and of 1500 mg/kg body weight and day for females were the NOAELs for effects on reproduction (ECHA 2014).

In a screening study that was carried out according to a modified version of OECD Test Guideline 421, 10 male and 10 female Sprague Dawley rats were exposed dermally (open exposure, at least 6 hours per day, collars to prevent ingestion) to hydrodesulfurized kerosene concentrations of 0% (sham exposure group with collars, vehicle control group), 20%, 40% or 60% (v/v) in mineral oil with a dose volume of 1 ml/kg body weight. The doses were 0, 165, 330 and 494 mg/kg body weight and day. The test substance was applied daily to the shaved skin of the animals, beginning 14 days before mating, during mating and throughout the 20 days of gestation. Male animals were treated for 1 week longer. Skin irritation was observed at 165 mg/kg body weight and day and above and was dependent on the concentration. Body weights and feed consumption were not impaired by the treatment. At 494 mg/kg body weight and day, body weight gains were reduced in the males. The relative kidney weights of the males of the high dose group were increased, which resulted from the lower final body weights. Histopathological examinations of the testes and epididymides as well as of the ovaries of the parental animals did not reveal substance-induced changes. There were no substance-induced effects on fertility, the number of live offspring, corpora lutea, implantation sites or body weights of the offspring. The highest dose of 494 mg/kg body weight and day was the NOAEL for parental toxicity and toxic effects on the offspring (ECHA 2014).

Groups of 5 male Sprague Dawley rats were exposed to jet fuel JP-8 vapour concentrations of 0, 250, 500 or 1000 mg/m^3 for 6 hours a day, for 91 days. Various testis proteins, such as heat shock protein 86, nicotinic acetylcholine receptor alpha subunit, serum albumin and T-complex protein 1, were increased compared with the levels in control animals (ECHA 2014). Histopathological examinations of the testes and sperm analysis were not carried out; it is therefore unclear whether the findings are to be regarded as adversefor the male reproduction.

Developmental toxicity

Studies of the toxic effects on prenatal development after the exposure of rats to petroleum distillates are shown in Table 3.

Groups of pregnant Sprague Dawley rats were exposed to **kerosene** concentrations of 0, 106 or 364 ml/m^3 for 6 hours a day, from days 6 to 15 of gestation. No adverse effects on the dams were observed, and there was no increase in the frequency of malformations, embryotoxicity or foetotoxicity, or any changes in the ratio between the sexes. Therefore, the NOAEC was 364 ml/m^3. The composition of the kerosene was not reported in the secondary source. Because of the high vapour concentration, the fraction of hydrocarbons with low boiling points was evidently higher. The original study is not available; the description was based on a secondary citation from the IUCLID for CAS number 64742-47-8 (ECB 2000 a in documentation "Distillates (petroleum), hydrotreated light" 2012).

An inhalation study with jet fuel A concentrations of 103 and 395 ml/m^3 did not reveal teratogenic effects on the offspring of Crl:COBS CD(SD)BR rats or maternal toxicity up to the highest concentration. Eye irritation was observed in 2 of 20 dams (control group), 7 of 20 dams (103 ml/m^3) and 20 of 20 dams (395 ml/m^3) (Beliles and Mecler 1982).

A NOAEL of 1000 mg/kg body weight was determined in a developmental toxicity study carried out with jet fuel JP-8 in Crl:CD rats according to OECD Test Guideline 414. Foetal weights were reduced at 1500 mg/kg body weight and above, and the body weight gains of the dams were decreased at 1000 mg/kg body weight and above. The animals received daily oral doses of undiluted JP-8 of up to 7.3 ml per animal (Cooper and Mattie 1996). At a density of 0.8 g/ml, the administered volume of 7.3 ml per animal corresponded to a dose of 5800 mg per animal. Assuming a target dose of 2000 mg/kg body weight, this yields a body weight for the rat of 2.9 kg, which is not plausible. This suggests that either the volume or the dose was incorrectly reported. The stomach capacity of an adult female Wistar rat is 3.4 ml. The recommended maximum volume for gavage doses given to rats is 10 ml per kg body weight, which means 2 ml for a body weight of 200 g (McConnell et al. 2008). The administration of up to 40 ml/kg body weight is technically feasible (Diehl et al. 2001). A study according to OECD Test Guideline 401 in rats yielded an LD_{50} value higher than 25 ml/kg body weight. This corresponds to a volume of 6 ml per animal at a body weight of 250 g; no animal died at this concentration (ECHA 2014). In a gavage study carried out with JP-8 for 21 weeks, mortality did not occur in female rats at 1500 mg/kg body weight and day (ECHA 2014; see Section "Fertility"), whereas 3 animals died at this dose in the study of Cooper and Mattie (1996). This suggests that the doses actually administered were 10 times higher than those calculated by the authors. Body weight data were not reported for the study; the body weight gains of the control animals were 134 g from days 5 to 20 of gestation. Because of the large number of inconsistencies, this study has not been included in the evaluation.

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Table 3 Prenatal developmental toxicity studies with petroleum distillates

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 20 ♀	**GD 6–15**, 0, 106.4 ± 10.23, 364 ± 37.53 ml kerosene/m^3, inhalation, whole body, 6 hours/day, examination: GD 20, similar to OECD Test Guideline 414	**> 364 ml/m^3**: **NOAEC** developmental toxicity, **NOAEC** maternal toxicity foetuses/dams: no abnormalities distillation range not specified	ECB 2000 a
rat, CRL:COBS CD(SD)BR, 20 ♀	**GD 6–16**, 0, 102.5 ± 5.7, 394.7 ± 19.3 ml jet fuel A/m^3, distillation range of jet fuel A: 163°C–282°C, inhalation, whole body, 6 hours/day, examination: GD 20, similar to OECD Test Guideline 414	**103 ml/m^3 and above**: dams: eye irritation (103 ml/m^3: 7/20, 395 ml/m^3: 20/20, control group: 2/20); **> 395 ml/m^3**: **NOAEC** developmental toxicity, **NOAEC** systemic toxicity and maternal toxicity foetuses: no abnormalities dams: no systemic toxicity	Beliles and Mecler 1982
rat, Crl:CD, 30 ♀	**GD 6–15**, 0, 500, 1000, 1500, 2000 mg jet fuel JP-8/kg body weight and day, gavage, volume: 1.1 ml to 7.3 ml, control group: 1 ml sterile water, examination: GD 20, similar to OECD Test Guideline 414	**500 mg/kg body weight**: **NOAEL** maternal toxicity; **1000 mg/kg body weight**: **NOAEL** developmental toxicity; **1000 mg/kg body weight and above**: dams: body weight gains (GD 5–20: 31%, 1500 mg/kg body weight: 0%, 2000 mg/kg body weight: 85%) ↓, corrected body weights (body weight – organ weight of pregnant uterus) ↓; **1500 mg/kg body weight and above**: foetuses: body weights (♂: 15%, 2000 mg/kg body weight: 24%, ♀: 13%, 2000 mg/kg body weight: 24%) ↓ dams: 13 deaths (1000 mg/kg body weight: 1, 1500 mg/kg body weight: 3, 2000 mg/kg body weight: 9) resulting from oil in lungs; deviation from Test Guideline: feed consumption not recorded; doses presumably miscalculated; not included in the evaluation because of considerable inconsistencies	Cooper and Mattie 1996

Genotoxicity

In vitro

A product free of aromatics with a distillation range of 205°C to 237°C was not found to be genotoxic in the Salmonella mutagenicity test. Likewise, a product free of aromatics with a distillation range of 240°C to 267°C was not genotoxic in the chromosomal aberration test with CHO cells (a cell line derived from Chinese hamster ovary). Negative results were obtained with hydrodesulfurized kerosene in the Salmonella mutagenicity test, the sister chromatid exchange (SCE) assay and the mouse lymphoma test in both the presence and absence of metabolic activation (documentation "Distillates (petroleum), hydrotreated light" 2012).

Various kerosenes were not mutagenic in the Salmonella mutagenicity test and in the mouse lymphoma test in the presence and absence of metabolic activation (ECHA 2014). A positive result was obtained for straight-run kerosene with TA 98 with metabolic activation. Hydrotreated kerosene and jet fuel A were not mutagenic in the Salmonella mutagenicity test in the presence and absence of metabolic activation (ECHA 2014).

In vivo

Hydrodesulfurized kerosene doses of 0, 400, 2000 or 4000 mg/kg body weight increased the incidence of SCE (sister chromatid exchange) in the bone marrow cells of male, but not of female B6C3F1-mice; the determination was carried out 20 to 22 hours after intraperitoneal injection (no other details; documentation "Distillates (petroleum), hydrotreated light" 2012).

Hydrodesulfurized kerosene doses of 0, 300, 1000 or 3000 mg/kg body weight did not increase the incidence of chromosomal aberrations in the bone marrow cells of SpragueDawley rats 6, 24 and 48 hours after intraperitoneal injection (documentation "Distillates (petroleum), hydrotreated light" 2012).

Straight-run kerosene did not induce chromosomal aberrations in the bone marrow of rats up to 3000 mg/kg body weight 6, 24 or 48 hours after single intraperitoneal injections. Encrusted eyes and noses and diarrhoea were detected in all animals of the high dose group. In this group, 3 of the 18 males died (ECHA 2014). Likewise, straight-run kerosene did not induce micronuclei in the bone marrow of male rats 6, 24 or 48 hours after single intraperitoneal injections of 0.04, 0.13 or 0.4 ml or after subchronic exposure (no other details) to 0.02, 0.06 or 0.18 ml per animal (ECHA 2014).

A dominant lethal test in rats (intraperitoneal injection) and mice (subcutaneous injection) with deodorized kerosene in a dose of 1 ml/kg body weight (about 800 mg/kg body weight) yielded negative results. Jet fuel A did not induce dominant lethal mutations in groups of 12 male mice that inhaled 100 or 400 ml/m^3 for 6 hours a day, on 5 days a week, for 8 weeks (ECHA 2014).

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Conclusion

Kerosene is not genotoxic in vitro or in vivo.

Carcinogenicity

Inhalation

In a 12-month study with a 1-year recovery period, groups of 50 male and 50 female F344 rats and C57BL/6 mice were exposed to jet fuel JP-4 concentrations of 0, 1000 or 5000 mg/m³ in whole-body exposure chambers for 6 hours a day, on 5 days a week. JP-4 is a mixture of petrol and kerosene; according to the gas chromatogram in the publication, the major fraction was C9–C14 hydrocarbons. In male rats, 5 kidney tumours caused by alpha2u nephrotoxicity were observed at 5000 mg/m³. In the males of this group also increased incidences of interstitial testis tumours (95%; control animals: 86%) and fibroadenomas of the mammary gland were observed. The incidence of pituitary tumours was increased in the females at 5000 mg/m³, whereas it was reduced in the males. Increased tumour incidences were found either only in organs with a high spontaneous incidence or with a reverse trend in the two sexes; they are thus not clearly dose-dependent, but statistically significant. In the rat lung, neither toxicity nor a significantly increased incidence of tumours was observed. The non-neoplastic effects on the kidneys (medullary mineralization and hyperplasia of the renal pelvis) were probably caused by alpha2u nephropathy because these effects were not observed in the females. In the female rats, the incidence of cystic hyperplasia of the mammary gland was increased at 5000 mg/m³. In rats and mice, increased hyperplasia in the lacrimal gland was observed at 1000 mg/m³ and above, but this was not concentration-dependent and no adverse concentration-dependent effects were found in the nasal turbinates; therefore, this finding is of unclear relevance. At 5000 mg/m³, the incidence of liver adenomas was increased in female mice. Many of the treated and untreated mice were found to have ulcerative dermatitis that was not dependent on the concentration and showed signs of a chronic systemic infection (granulocytic hyperplasia in the bone marrow). The number of animals evaluated varied in the individual exposure groups; therefore, it is difficult to evaluate the non-neoplastic effects of the substance (inflammatory infiltrates in the liver) in mice. In addition, at 1000 mg/m³ and above, testicular atrophy was found in the males and islet cell hyperplasia in the females, but these findings were not dependent on the concentration (Bruner et al. 1993).

Dermal application

Studies with epicutaneous application are shown in Table 4.

Table 4 Dermal carcinogenicity studies in mice with various kerosenes

Substance distillation range	Application dose (at 0.03 kg assumed body weight)	Strain number per dose	Findings	References
Initiation and promotion studies				
jet fuel A 21.8% aromatics 163°C–273°C	**promotion study** DMBA as initiator, jet fuel A as promoter 1. DMBA – undiluted jet fuel A, 37.5 µl 2×/week 2. DMBA – 28.6% jet fuel A in mineral oil, 37.5 µl 7×/week 75 µl jet fuel A/week, about 2000 mg/kg body weight/week 3. DMBA – mineral oil 52 weeks	CD-1 30 ♂	1. irritation index: 2.12 of 4 2 animals with a squamous cell carcinoma, 1 animal with a keratoacanthoma, 10 animals with a papilloma 2. irritation index: 0.18 of 4 1 animal with a lymphosarcoma 3. irritation index: 0.03 of 4 1 animal with a squamous cell carcinoma	Nessel et al. 1999
hydrodesulfurized kerosene (42.7% paraffins, 1% olefins, 19.3% monocycloparaffins, 18.9% dicycloparaffins, 14.7% alkylbenzenes, 7.5% indanes/tetralins, 0.6% naphthalene, 6.3% naphthalenes, < 50 mg PAHs/kg) 175°C–279°C 64742-81-0	**promotion study** 1. 1× 50 µg DMBA as initiator, 25, 50, 100 µl kerosene as promoter, 2×/week, 25 weeks 2. 1× 50 µg DMBA as initiator, 50 µl kerosene as promoter, 2×/week, 25 weeks, 1 hour before kerosene: 15 µg dexamethasone 5×/week 3. 1× 50 µg DMBA 4. 5× 50 µl kerosene, 50 µl kerosene as the promoter 2×/week, 25 weeks	CD-1 30–54 ♂	1. grade of acanthosis 1.2, 1.6, 2.0 of 4 25 µl: 26% (of these 1 squamous cell carcinoma), 50 µl: 24% and 100 µl: 66% (of these 2 squamous cell carcinomas) animals with tumours 2. 0% animals with tumours 3. 0% animals with tumours 4. 0% animals with tumours	Skisak 1991

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Table 4 (continued)

Substance distillation range	Application dose (at 0.03 kg assumed body weight)	Strain number per dose	Findings	References
hydrodesulfurized kerosene (47% paraffins, 1% olefins, 35% naphthenes, 18% aromatics) 183°C–279°C 64742-81-0	**initiation-promotion study** 1. 50 µl kerosene as initiator for 5 days, PMA as promoter 1×/week, 25 weeks, initiation control: acetone or toluene 2. 50 µl 0.1% DMBA as initiator, 50 µl kerosene as promoter, 2×/week, 25 weeks, promotion control: toluene	CD-1 30 ♂	1. acetone PMA: 3/30 with tumours, toluene PMA: 8/29 with tumours, kerosene PMA: 3/30 with tumours 2. DMBA toluene: 2/30 with tumours, DMBA kerosene: 22/30 with tumours hydrodesulfurized kerosene is not an initiator but a skin tumour promoter	Skisak et al. 1994
Long-term studies				
jet fuel A 180–271°C	undiluted, 3×/week, 25 mg/animal, about 800 mg/kg body weight, 62 weeks, recovery period up to week 105 negative control: mineral oil	C3H 25 ♂, 25♀	irritation: inflammation as of 2 months after application mortality, necrosis as of 1 year after application; exposure was terminated as a result tumours: 9% squamous cell carcinomas, 12% fibrosarcomas controls: no irritation, no tumours	Clark et al. 1988
jet fuel A 21.8% aromatics 163°C–273°C	undiluted, 2×/week (or intermittent to reduce irritation), 37.5 µl kerosene (about 30 mg/animal), about 1000 mg/kg body weight, 104 weeks negative control: untreated animals	C3H 50 ♂	irritation: in the treated animals tumours: 2×/week: 44% of the animals (of 50) had skin tumours, intermittent: 1/50 with a skin tumour, controls: 0% → authors: decrease in irritation also reduced tumour incidences, but this may also have been the result of the lower dose	Freeman et al. 1993

Table 4 (continued)

Substance distillation range	Application dose (at 0.03 kg assumed body weight)	Strain number per dose	Findings	References
hydrotreated straight-run kerosene 17.1% aromatics no PAHs detectable (detection limit: < 0.1%) 84°C–291°C 64742-81-0	undiluted, 2×/week, 50%, 4×/week, 28.5%, 7×/week, 50 µl kerosene/week (about 40 mg/animal) about 1300 mg/kg body weight, 104 weeks vehicle and negative control: mineral oil	C3H 50 ♂	irritation: severe irritation caused by undiluted kerosene; in the case of diluted kerosene, irritation was slight, as in the case of mineral oil tumours: undiluted: 11 animals with malignant skin tumours, 6 with papillomas, no tumours after 50% and 28.5% and in controls → authors: promotion effect, skin irritation is essential for tumour development	Nessel et al. 1998
hydrodesulfurized kerosene (47% paraffins, 1% olefins, 35% naphthenes, 18% aromatics) 183°C–279°C 64742-81-0	undiluted, 2×/week, 50 µl kerosene (about 40 mg/animal), about 1300 mg/kg body weight, 104 weeks negative control: untreated animals	C3H 50 ♂, 50 ♀	irritation: in the treated animals tumours: 46% of animals (of 41 included in the final evaluation) had malignant skin tumours controls: 0%	Skisak et al. 1994
straight-run kerosene (2 samples) and hydrotreated kerosene	undiluted, 2×/week, 50 mg kerosene/animal, about 1666 mg/kg body weight, 104 weeks or until papillomas > 1 mm^2 developed negative control: untreated animals	C3H 50 ♂	straight-run kerosene: irritation: no other details tumours with the 2 samples: 9/30 or 4/27 with papillomas hydrotreated kerosene: irritation: no other details tumours: 24/38 with papillomas, controls: 0% → hydrogenated product caused higher number of tumours	ECHA 2014

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Table 4 (continued)

Substance distillation range	Application dose (at 0.03 kg assumed body weight)	Strain number per dose	Findings	References
straight-run kerosene contains no relevant amounts of known carcinogens, for example PAHs 8008-20-6	undiluted, 2×/week, 50 µl kerosene (about 40 mg/animal), about 1300 mg/kg body weight, 104 weeks negative control: untreated animals	C3H 50 ♂	irritation: desquamation and alopecia in the treated animals tumours: benign: 1/45, malignant: 25/45 animals controls: 0% → authors: tumours resulted from skin irritation	ECHA 2014
JP 5 navy fuel (52.8% cycloparaffins, 30.8% paraffins, 15.9% aromatics, 0.5% olefins)	in acetone, 5×/week, 0, 250, 500 mg JP5/kg body weight, 90 weeks (♀) or 103 weeks (♂) negative control: vehicle control	B6C3F1 50 ♂, 50 ♀	irritation: in treated animals and vehicle controls, severity dose-dependent, treatment in females terminated after 90 weeks because of excessive irritation tumours: incidence not significantly increased, 1 ♂ and 1 ♀ with a squamous cell carcinoma in the high dose group	NTP 1986

DMBA: dimethylbenzanthracene; PAHs: polycyclic aromatic hydrocarbons; PMA: phorbole 12-myristate 13-acetate

Conclusions

Undiluted kerosenes caused carcinogenicity and irritation to the skin in mice in all studies in which undiluted kerosenes were tested. Hydrodesulfurized kerosene and jet fuel A did not act as initiators, but as promoters in the mouse skin. A study (Nessel et al. 1998) positively correlated the number of tumours with irritation at the same total weekly dose. Thus, if irritation was avoided by dilution while the frequency of application was correspondingly increased, tumours did not occur despite the same weekly dose having been applied. In the NTP study (NTP 1986), skin tumours were not observed in B6C3F1 mice although a weekly dose of 5 × 500 mg/kg body weight = 2500 mg/kg body weight was used and marked irritation was observed. In the studies with positive results, C3H mice were used and the weekly dose was about 2500 to 3000 mg/kg body weight. C3H mice thus appear to be much more sensitive than B6C3F1 mice. However, in the same NTP study, B6C3F1 mice developed skin tumours after the application of diesel oil. This demonstrates that this strain of mice is actually susceptible to this type of tumour formation. The extent to which the treatment of kerosene with hydrogen has an influence on the tumourigenic effects is unclear. In one study, a hydrotreated kerosene was more tumourigenic than a straight-run kerosene (ECHA 2014). A PAH content below 0.1% was apparently not responsible for the tumours because mineral oils with PAH levels below 1% were neither mutagenic in the Ames test nor carcinogenic in the long-term study in mouse skin (Roy et al. 1988). This assumption is also supported by the fact that the examined kerosenes had no initiating effects. However, up to 0.15% naphthalene was detected in jet fuels. The specification allows for substituted naphthalene levels of up to 3% (Shafer and Edwards 2011).

The studies used high purity mineral oils consisting of hydrocarbons > C15 as negative controls. These do not cause irritation or carcinogenicity to the skin. Therefore, skin irritation or carcinogenicity may have been caused by the physical properties of the C9 to C15 hydrocarbons. There are no studies available in species other than mice.

Manifesto (MAK value/classification)

MAK value. In a 13-week inhalation study carried out in Wistar rats with a product free of aromatics (C10–C12 isoparaffins, 170°C to 187°C), increased liver weights were found as the most sensitive end point at the lowest concentration of 359 ml/m^3 and above, but no histopathological or clinico-chemical (ASAT/ALAT) effects were detected. The weights were increased by less than 10% at 359 ml/m^3, by 14% at 737 ml/m^3 and by about 40% at 1444 ml/m^3. After exposure at the high concentration, CNS effects in the form of lethargy were found. However, no conclusions can be drawn from animal studies as to which concentration would cause CNS and irritative effects in humans, such as were induced by other hydrocarbon mixtures such as white spirit. As stated in the introduction, white spirit can be

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viewed as representative for "hydrotreated light distillates (petroleum)". Therefore, based on volunteer studies with white spirit, a MAK value of 50 ml/m³ has been established by analogy to "hydrotreated heavy naphtha (petroleum)" (documentation "Naphtha (petroleum), hydrotreated heavy" 2010). The MAK value takes into account that the volunteers were exposed at rest and that there would be higher exposure to hydrocarbons at the workplace at an assumed higher respiration rate of 10 m³/8 hours.

Studies of kerosene aerosols (jet fuel) suggest that they might have a severer effect on the lungs than vapours. However, the data were obtained only after short-term subacute exposure (1 hour per day). A LOAEC or NOAEC after 8-hour exposure cannot be derived from these studies because an intensification of the effects is to be expected. An effect on the lungs is consistent with the effect caused by mineral oils, for which a long-term NOAEC of 5 mg/m³ was established (see documentation "White mineral oil, pharmaceutical" 2015). Therefore, until suitable studies are available for the aerosol fraction of "hydrotreated light distillates (petroleum)", the MAK value for white mineral oil (5 mg/m³ R) has been adopted because white mineral oil also consists of hydrocarbons, but with an even higher carbon number.

Peak limitation. The MAK value is based on systemic toxicity. Specific data for the determination of an excursion factor are lacking. Peak Limitation Category II with a default excursion factor of 2 has been established for the vapour fraction of "hydrotreated light distillates (petroleum)" (documentation "Distillates (petroleum), hydrotreated light" 2012) by analogy to "hydrotreated heavy naphtha (petroleum)".

An excursion factor of 4 has been established for the aerosol fraction by analogy to pharmaceutical white mineral oil (see documentation "White mineral oil, pharmaceutical" 2015).

Prenatal toxicity. Inhalation studies in rats with kerosene and jet fuel did not reveal developmental or systemic maternal toxicity up to the highest concentrations of 364 and 395 ml/m³, respectively. The actual NAEC (no adverse effect concentration) for developmental toxicity in rats is presumably even higher than 395 ml/m³, which was the highest concentration used in the inhalation studies. Therefore, it is at least 8 times higher than the MAK value. As the NAEC of developmental toxicity is higher than 395 ml/m³ and the structure does not suggest teratogenicity, classification in Pregnancy Risk Group C has been retained for "hydrotreated light distillates (petroleum)".

Carcinogenicity. In initiation-promotion tests, hydrodesulfurized kerosene (Skisak et al. 1994) and jet fuel A (Nessel et al. 1999) did not act as initiators, but as promoters. In all long-term studies in which undiluted kerosenes were tested without an initiator they caused carcinogenicity (for example squamous cell carcinomas) and irritation to the skin of mice. The tumours were observed only with undiluted kerosene, which also induced skin irritation, but not with diluted kerosene that caused neither skin irritation nor tumours. Doses of at least 1000 mg/kg

body weight were applied twice a week. As the relevance of these skin tumours for humans is still unclear, classification in Carcinogen Category 3B has been retained.

Germ cell mutagenicity. There is no evidence to date for germ cell mutagenicity of hydrodesulfurized kerosene. Likewise, studies with other kerosenes did not reveal evidence of genotoxicity in vitro or in vivo. "Hydrotreated light distillates (petroleum)" are not classified in any of the germ cell mutagen categories.

Absorption through the skin. It was estimated from an in vitro study with rat skin after 1-hour exposure to 40 mg that a very low amount of C7–C17 hydrocarbons (including aromatics) would be absorbed compared with the amount absorbed (about 2100 mg at 60% absorption and 10 m^3 respiratory volume) after exposure to 50 ml/m^3 (350 mg/m^3), the level of the MAK value for systemic effects. As "hydrotreated heavy naphtha (petroleum)" has not been designated with an "H", "hydrotreated light distillates (petroleum)" have not been designated with an "H" (documentation "Distillates (petroleum), hydrotreated light" 2012).

Sensitization. Other than the negative results in a Buehler test described in the 2012 documentation (documentation "Distillates (petroleum), hydrotreated light" 2012), no new data have become available from humans or animals for sensitizing effects on the skin or respiratory tract; therefore, "hydrotreated light distillates (petroleum)" have not been designated with "Sh" or "Sa".

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