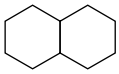
Decahydronaphthalene[1)]

MAK value (2014)	**5 ml/m³ ≙ 29 mg/m³**
Peak limitation (2014)	**Category II, excursion factor 2**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2014)	**Pregnancy Risk Group D**
Germ cell mutagenicity	**–**
BAT value	**–**
Synonyms	bicyclo[4.4.0]decane decahydronaphthalene naphthalane naphthane perhydronaphthalene
Chemical name	decahydronaphthalene
CAS number	493-01-6 (*cis*-decalin) 493-02-7 (*trans*-decalin) 91-17-8 (isomer mixture)
Structural formula	
Molecular formula	$C_{10}H_{18}$
Molecular weight	138.25
Melting point	–43°C (*cis-decalin*) (BUA 2000) –30°C (*trans-decalin*) (BUA 2000) –40°C (isomer mixture) (BUA 2000)

1) The substance can occur simultaneously in vapour and aerosol form

Boiling point at 1013 hPa	195°C (*cis-decalin*) (BUA 2000)
	187°C (*trans- decalin*) (BUA 2000)
	189–191°C (isomer mixture) (BUA 2000)
Density at 20°C	0.8963 g/cm^3 (*cis-decalin*) (IFA 2013)
	0.8700 g/cm^3 (*trans-decalin*) (IFA 2013)
	0.88 g/cm^3 (isomer mixture) (IFA 2013)
Vapour pressure at 25°C	1.04 hPa (*cis-decalin*) (SRC 2014 a)
	1.63 hPa (*trans- decalin*) (SRC 2014 b)
	3.07 hPa (isomer mixture) (SRC 2014 c)
log K_{OW}	4.2 (calculated) (SRC 2014 a, b, c)
octanol/water partition coefficient	
Solubility	1.41 mg/l water at 21°C (*cis-decalin*) (BUA 2000)
	0.889 mg/l water at 25°C (isomer mixture) (BUA 2000)
1 ml/m^3 (ppm) ≙ 5.74 mg/m^3	**1 mg/m^3 ≙ 0.174 ml/m^3 (ppm)**

This documentation is primarily based on a BUA report and an NTP report (BUA 2000; NTP 2005).

1 Toxic Effects and Mode of Action

Decahydronaphthalene was found to be corrosive to the rabbit skin, whereas it did not cause irritation in the rabbit eye. Repeated inhalation exposure to decahydronaphthalene and ingestion of the substance caused α_{2u}-globulin nephropathy in male rats. Increased LDH (lactate dehydrogenase) activity was observed in the urine of female rats at 25 ml/m^3 and above. After inhalation, centrilobular cytomegaly in the liver and syncytial alteration were observed in male mice at 50 ml/m^3 and above, and the liver weights were increased in mice of both sexes at 100 ml/m^3 and above.

Decahydronaphthalene was not found to be genotoxic in vitro in genotoxicity tests. In the only valid in vivo micronucleus test in mice, the incidence of micronuclei was slightly increased in male mice after inhalation exposure, but decahydronaphthalene is nevertheless not considered to be genotoxic.

In carcinogenicity studies in rats and mice with inhalation exposure to decahydronaphthalene, male F344 rats were found to have neoplasms in the kidneys which were caused by an accumulation of α_{2u}-globulin. Increased incidences of hepatocellular carcinomas were found in female B6C3F1 mice, but only at the low concentration.

In the offspring of female mice treated with decahydronaphthalene, toxic effects on development were not detected up to day 3 of life.

Decahydronaphthalene did not cause sensitization in a maximization test carried out according to the guidelines.

2 Mechanism of Action

Nephrotoxicity, kidney tumours

In the kidneys of male rats, decahydronaphthalene induced progressive neoplasms characteristic of the species and sex-specific α_{2u}-globulin nephropathy. This is supported by the fact that inhalation exposure to decahydronaphthalene caused the accumulation of α_{2u}-globulin and hyaline droplets in the kidneys only in male rats, but not in female rats or male and female mice (NTP 2005). Lysosomal protein degradation is presumably disturbed by the binding of decahydronaphthalene or one of its metabolites, for example decalone, to α_{2u}-globulin in the kidney cells. The accumulation of protein droplets induced necrosis in the proximal tubules, the formation of granular casts and, in the course of time, increased cell proliferation. In addition, the accumulation of calcium hydroxylapatite in the thin section of Henle's loop (renal papillary mineralization) was observed. These histopathological changes finally induced neoplastic lesions in the kidneys of male rats (NTP 2005). This type of nephropathy is specific to male rats and therefore not relevant to humans (Hard et al. 1993). However, the increase in LDH in the urine of female rats suggests there is another unknown mechanism of nephrotoxicity also in female rats (NTP 2005).

Hepatotoxicity

The mechanism of hepatotoxicity induced by decahydronaphthalene is not known (Stuchal et al. 2013).

Local effects on skin and mucous membranes

Undiluted decahydronaphthalene was corrosive to the skin of rabbits. However, decahydronaphthalene did not cause irritation in the rabbit eye (see Section 5.3).

This result can be explained by the pronounced defatting effect of decahydronaphthalene. In the tests for skin irritation, decahydronaphthalene was in contact with the skin for 4 hours; sufficient time for the defatting effect to take place. In the eyes, the tear film protects against defatting and the substance is washed out by blinking. A corrosive substance would induce effects on the edge of the eyelid. This type of effect has not been described for decahydronaphthalene.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution and elimination

Male and female F344/N rats and around 12-week-old B6C3F1 mice were exposed once to decahydronaphthalene concentrations of 25, 100 or 400 ml/m^3 by inhalation (whole-body exposure) for 6 hours. The decahydronaphthalene used was a mixture of 35% *cis*-decalin and 65% *trans*-decalin. Blood samples were taken at different times between 5 minutes and 24 hours, and the kidneys were removed from 3 male rats after 2, 4, 8 and 24 hours. The decahydronaphthalene concentration in the blood at the end of exposure was independent of the sex, but was concentration-dependent. Elimination was characterized by two-phase kinetics. A rapid initial phase representing elimination from the blood and highly perfused organs such as the liver, lungs and kidneys was followed by a slower terminal phase involving elimination from muscles and adipose tissue. There were no statistically significant differences between the sexes as regards the half-times of the two elimination phases, although the half-times were somewhat longer in female rats at 100 ml/m^3 and above. In mice, the initial half-times of 5.8 to 26 minutes were 1 to 6 times shorter than those in rats (initial: 23–38 minutes) and the terminal half-times of 95 to 131 minutes were 3 to 5 times shorter (terminal: 418–546 minutes in rats); this indicates faster metabolism or elimination in mice. Elimination kinetics that is not proportional to the dose suggests non-linear toxicokinetic behaviour at higher exposure concentrations. On the basis of the ratio between the AUC (area under the blood concentration–time curve) and the exposure concentration, the authors concluded that male rats were able to eliminate decahydronaphthalene from circulating blood faster than female rats. In mice, the investigations did not provide any evidence of sex-specific differences as regards the elimination of decahydronaphthalene from the blood. In the kidneys of male rats, the decahydronaphthalene concentration was highest after 2 hours and at the later time points decreased continuously, except in the group exposed to 400 ml/m^3. With the increasing exposure concentrations there was a disproportionate increase in the decahydronaphthalene concentration in the kidneys. The concentrations in the kidneys of the females were considerably lower, increased proportionally in relation to the exposure concentration and after exposure decreased continuously over a period of 24 hours. The concentrations of the metabolite decalone and α_{2u}-globulin in the kidneys of male rats were hardly related to time and the concentration. In the females, the decalone concentrations were close to or below the limit of quantification, and the α_{2u}-globulin concentrations were 1000 times lower than in the males. According to a PBPK model, the significant differences between male and female rats resulted from different decahydronaphthalene concentrations in the kidneys. The model predicted a higher rate of metabolism in mice, but the metabolism was saturated earlier in mice than in rats. At the highest concentration used of 400 ml/m^3, metabolism was saturated in both rats and mice. The only difference in male and female rats was the binding to α_{2u}-globulin (Dill et al. 2003; NTP 2005).

In a comparative study, young F344/N rats of around 12 weeks old and F344/N rats of around 22 months old of both sexes were exposed once by inhalation (whole-body exposure) to decahydronaphthalene concentrations of 25 or 400 ml/m^3 (35% *cis*-isomer and 65% *trans*-isomer). Blood samples were taken at different times between 0 and 16 hours after exposure. After blood sampling, the animals were sacrificed and the kidneys were removed. In addition, the pooled 16-hour urine samples were examined. The decahydronaphthalene concentrations in blood increased disproportionately in all groups immediately after exposure. After 16 hours, the concentrations were significantly reduced. Sex-specific differences were not observed. There were no age-related differences regarding the toxicokinetic parameters for the elimination of decahydronaphthalene from the blood. Higher concentrations of the metabolite decalone were determined in the kidneys of young male rats than in those of old males or all the female rats, and the concentrations did not decrease within 16 hours. In the old males and all the female rats, the decalone concentrations in the kidneys were in the range of the limit of quantification and decreased markedly within 16 hours. Compared with the levels in young male rats, the α_{2u}-globulin concentrations in the kidneys were about 100 times lower in old males and about 1000 times lower in all the females. The concentrations of the metabolite decalol in relation to creatinine in the pooled 16-hour urine increased proportionally to the increase in the exposure concentration. This increase was disproportionate in young male rats, and the concentrations in the urine were always lower than in the other groups, particularly in the group exposed to 400 ml/m^3. According to the authors, this effect was the result of the retention of decahydronaphthalene and decalone in the kidneys of young male rats (Dill et al. 2003).

Young male F344/N rats of around 11 weeks old were given single intravenous injections of *cis-decalin* or *trans-decalin* in doses of 0, 2.5, 5, 10 or 20 mg/kg body weight. The kidneys were removed and examined after 16 hours. It was generally found that after administration of *cis-decalin* about 2 to 3 times more decalone had bound to α_{2u}-globulin in the kidneys than after administration of *trans-decalin*. The molar ratio between α_{2u}-globulin and the sum of decahydronaphthalene and decalone in the kidneys was about 1.0 (Dill et al. 2003).

Using the models of Fiserova-Bergerova et al. (1990), Guy and Potts (1993) and Wilschut et al. (1995), it was calculated that the exposure of 2000 cm^2 skin to a saturated aqueous solution of decahydronaphthalene for 1 hour would result in absorbed amounts of 49.9, 0.703 and 0.234 mg at a log K_{OW} of 4.2, molecular weight of 138.25 g/mol and water solubility of 0.00141 g/l. Undiluted decahydronaphthalene is corrosive to the skin, but the concentration of the saturated aqueous solution is so low that it probably no longer causes irritation of the skin.

3.2 Metabolism

Figure 1 shows the metabolism of decahydronaphthalene.

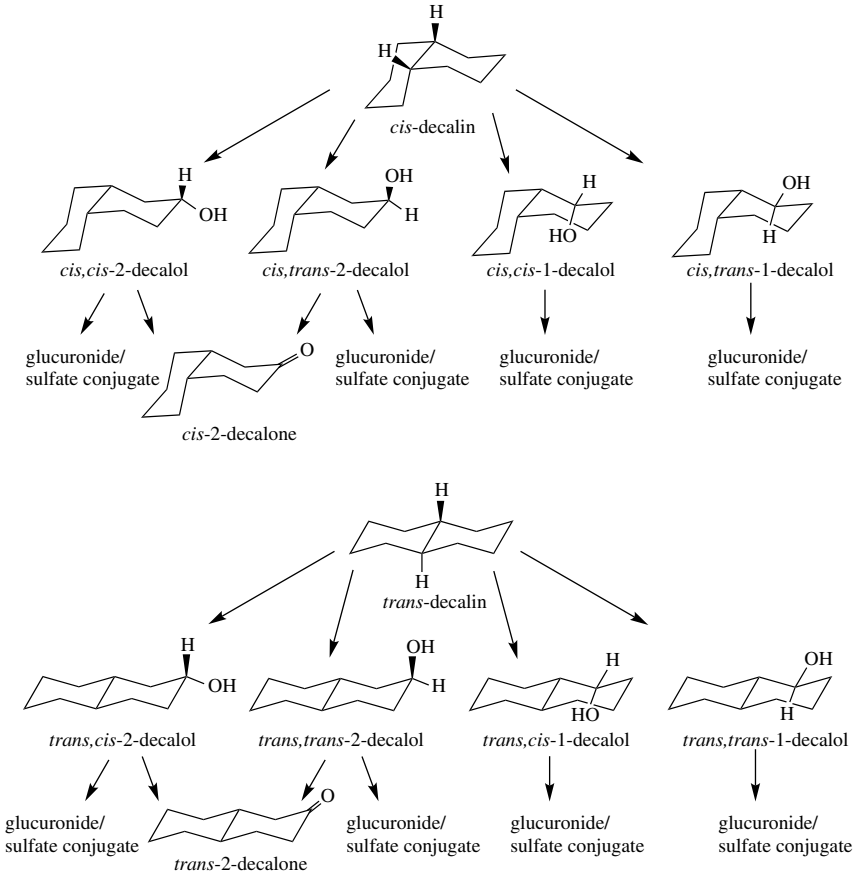


Figure 1 The metabolism of decahydronaphthalene (Dill et al. 2003)

The substance was eliminated as *cis*,*cis*-2-decalol (main metabolite) and as *cis*, *trans*-1-decalol in the urine of female and male F344 rats that had ingested a *cis-decalin* dose of 3000 mg/kg body weight every second day for 14 days. In addition, *cis*,*cis*-1-decalol was found in the urine of the males. After the administration of 2500 mg *trans-decalin*, *trans*,*cis*-2-decalol was the main metabolite in the urine and *trans*,*trans*-1-decalol was determined only in the males. The metabolites were found in the urine in glucuronidated or sulfated form. After the administration of *cis-decalin* or *trans-decalin* to animals of both sexes, *cis*-2-decalone or *trans*-2-decalone were detected only in the kidney homogenate of the males (BUA 2000).

In female rabbits, *cis-decalin* was metabolized mainly to *cis*,*cis*-2-decalol and, to a lesser extent, to *cis*,*trans*-2-decalol after oral administration. *Trans-decalin* was metabolized mainly to *trans*,*cis*-2-decalol and, only to a slight extent, to *trans*,*trans*-2-

decalol. The alcohols were eliminated with the urine in the form of glucuronides in amounts equivalent to 60% of the administered dose. Unlike in rats, no 1-decalol compounds were identified (BUA 2000; NTP 2005).

After rats were exposed to decahydronaphthalene once by inhalation or intravenous injection (see Section 3.1), both decahydronaphthalene and decalone were detected in the kidneys of the males (Dill et al. 2003).

4 Effects in Humans

There are no studies available in humans of the genotoxicity, carcinogenicity, reproductive toxicity, or allergenic effects of decahydronaphthalene, or of the effects after repeated exposure.

In humans, irritation (no other details in the secondary citation) was found after inhalation exposure to 100 ml/m^3 (575 mg/m^3) (Gaworski et al. 1985).

Decahydronaphthalene was described as having irritating effects on the eyes, skin and mucous membranes (BUA 2000; NTP 2005).

Liquid alicyclic compounds, such as decahydronaphthalene, dehydrate and defat the skin and cause dermatitis (NLM 2013).

After skin contact with decahydronaphthalene, a man who cleaned paving stones was found to have vesicular eczema accompanied by marked itching on the most exposed areas of the forearms and sacral area. Skin tests demonstrated "sensitivity" to decahydronaphthalene (no other details) (NLM 2013).

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

Deaths were not observed after the exposure of rats for up to 2 hours to saturated decahydronaphthalene vapour (theoretical concentration: 1150 ml/m^3 or 6612 mg/m^3) (BUA 2000).

In rats, the LC_{50} after exposure for 4 hours was 5740 mg/m^3 (1000 ml/m^3) (BUA 2000). Another study in male rats yielded a 4-hour LC_{50} of 4080 mg/m^3 (710 ml/m^3) (BUA 2000). An LC_{50} of 2870 mg/m^3 (500 ml/m^3) was reported after exposure to decahydronaphthalene for 1 hour (BUA 2000).

In female mice, the 4-hour LC_{50} was 6230 mg/m^3 (1085 ml/m^3) (BUA 2000).

Tremor and convulsions, followed by prostration, were observed in rats and mice after exposure to decahydronaphthalene. In the surviving rats, paralysis of the hind extremities was observed. The pathological examination revealed congestion of the lungs with some atelectatic areas (BUA 2000).

5.1.2 Oral administration

An LD_{50} of 4170 mg/kg body weight was reported in rats after oral administration (BUA 2000).

5.1.3 Dermal application

LD_{50} values of 5204 or 5900 mg/kg were determined in rabbits after dermal application (BUA 2000; NTP 2005).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

Studies of the toxic effects after repeated inhalation exposure to decahydronaphthalene are described in Table 1.

Table 1 Studies of the toxicity after repeated inhalation exposure to decahydronaphthalene

Species, strain, number per group	Exposure	Findings	References
rat, F344/N, 5 ♂, 5 ♀	**16 days**, 0, 25, 50, 100, 200, 400 ml/m³, 6 hours/day, 5 days/week	**25 ml/m³ and above**: ♂: kidneys: accumulation of hyaline droplets (concentration-dependent increase in severity), degeneration and regeneration of the renal tubules in 5/5 (concentration-dependent increase in severity), α_{2u}-globulin/protein ratio ↑; ♀: liver: absolute and relative weights ↑; **50 ml/m³ and above**: ♂: kidneys: absolute and relative weights ↑, granular casts ↑ (concentration-dependent increase in severity); liver: absolute weights ↑; **100 ml/m³ and above**: ♂: liver: absolute and relative weights ↑; **200 ml/m³ and above**: ♂: kidneys: PCNA labelling index and number of PCNA-positive cells ↑	NTP 2005
rat, NBR, 5 ♂	**16 days**, 0, 25, 50, 100, 200, 400 ml/m³, 6 hours/day, 5 days/week	**50 ml/m³**: liver: relative weights ↑; **100 ml/m³ and above**: liver: absolute and relative weights ↑	NTP 2005
rat, Alderley Park, 4 ♂, 4 ♀	**20 days**, 0, 200 ml/m³, 6 hours/day, 5 days/week	**200 ml/m³**: no signs of toxicity, no findings in the liver, lungs, spleen, kidneys or adrenal glands in the pathological examination; documentation of study inadequate	BUA 2000

Table 1 (Continued)

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 100 ♂	**30 days**, 0, 50, 250 ml/m^3, 6 hours/day, 5 days/week	**50 ml/m^3 and above**: body weights ↓, absolute lung, heart and liver weights ↓, relative kidney weights ↑, concentration-related histopathological changes in trachea, bronchi and alveoli (formation of hyaline droplets in the tracheal epithelium, loss of ciliated cells, proliferation of goblet cells), liver (hydropic changes in the cytoplasm), kidneys (hyaline droplets in the cytoplasm of the tubular epithelial cells) and bladder (cytoplasmic vacuolation); **250 ml/m^3**: tracheobronchial epithelium: exudate, type 2 alveolar cells ↑	MacEwen and Vernot 1978
rat, F344, 40 ♂	**5, 12, 19 or 31 days**, 0, 125 ml/m^3, 6 hours/day, 5 days/week (group 1) or 22 hours/day, 5 days/week (group 2) or 22 hours/day, 7 days/week (group 3)	**125 ml/m^3**: relative liver and kidney weights ↑ (in all groups on day 5 and thereafter); hyaline droplets in the proximal tubule cells (on day 5 and thereafter; severity: group 1 < 2 ≈ 3); tubular epithelial cells: degeneration/necrosis (in groups 2 and 3 on day 5 and thereafter); granular casts in the outer zone of the renal medulla (group 1: on day 19 and thereafter; groups 2 and 3: on day 12 and thereafter); incidence of chronic nephrosis ↑ (in all groups on day 12 and thereafter); histopathological examination of kidneys only	Kanerva et al. 1987
rat, F344, 30 ♂	**20, 28 or 35 days**, 0, 25, 62.5, 125 ml/m^3, 22 hours/day, 7 days/week	**25 ml/m^3 and above**: hyaline droplets in the proximal tubule cells, granular casts in the outer zone of the renal medulla and chronic nephrosis ↑ in relation to the dose and time; no histopathological findings in heart, liver, lung, nasal concha	Stone et al. 1987 a
rat, F344, 10 ♀	**28 days**, 0, 125 ml/m^3, 22 hours/day, 7 days/week	**125 ml/m^3**: no histopathological changes	Stone et al. 1987 a

Table 1 (Continued)

Species, strain, number per group	Exposure	Findings	References
rat, F344, 75 ♂, 75 ♀	**90 days**, 0, 5, 50 ml/m³, continuous, examination after 90 days (25 ♂, 25 ♀) or after up to 24 months	**5 ml/m³ and above**: ♂: body weights ↓; kidneys: nephrosis, tubular necrosis, formation of hyaline droplets; recovery period: ♂: kidneys: CPN ↑ (controls: 80%, 5 ml/m³: 100%, 50 ml/m³: 100%), mineralization ↑, hyperplasia of renal pelvis urothelium ↑; pituitary adenomas ↑ (controls: 10%, 5 ml/m³: 33%, 50 ml/m³: 33%); **50 ml/m³**: ♂: absolute and relative kidney weights ↑; recovery period: ♀: kidneys: CPN ↑ (controls: 27%, 5 ml/m³: 26%, 50 ml/m³: 51%); no irritation of the respiratory tract	Gaworski et al. 1985
rat, F344/N, 10 ♂, 10 ♀; satellite groups: 2 weeks 5 ♂ for nephrotoxicity; 6 weeks 10 ♂, 10 ♀ for clinical pathology	**14 weeks**, 0, 25, 50, 100, 200, 400 ml/m³, 6 hours/day, 5 days/week	**25 ml/m³ and above**: ♂: kidneys: relative weights ↑, accumulation of hyaline droplets (concentration-dependent increase in severity), renal tubule regeneration in 10/10, PCNA labelling index and number of PCNA-positive cells ↑; urine: glucose/creatinine ratio ↑, protein/creatinine ratio ↑, AST/creatinine ratio ↑, LDH/creatinine ratio ↑; ♀: urine: LDH/creatinine ratio ↑; LOAEC; **50 ml/m³ and above**: ♂: kidneys: relative weights ↑, granular casts ↑ (concentration-dependent increase in severity); liver: relative weights ↑; ♀: urine: AST/creatinine ratio ↑; **100 ml/m³ and above**: ♂: kidneys: α_{2u}-globulin concentration ↑ (after 14 weeks); **200 ml/m³ and above**: ♂: kidneys: absolute and relative weights ↑, α_{2u}-globulin concentration and α_{2u}-globulin/protein ratio ↑ (after 2, 6 and 14 weeks); liver: absolute and relative weights ↑; **400 ml/m³**: ♀: liver: relative weights ↑	NTP 2005
rat, F344/N, 50 ♂, 50 ♀, 20 ♂ at 400 ml/m³	**105 weeks**, 0, 25, 50 (only ♂), 100, 400 ml/m³, 6 hours/day, 5 days/week	**25 ml/m³**: ♂: kidneys: accumulation of hyaline droplets, tubular hyperplasia (11/50), papillary mineralization (34/50), hyperplasia of transitional epithelium of the renal pelvis (8/50); **50 ml/m³**: ♂: kidneys: tubular hyperplasia (11/49), papillary mineralization (41/49) and hyperplasia of the transitional epithelia of the renal pelvis (8/49); adrenal medulla: hyperplasia (26/49);	NTP 2005

Table 1 (Continued)

Species, strain, number per group	Exposure	Findings	References
		100 ml/m³: ♂: kidneys: accumulation of hyaline droplets, tubular hyperplasia (15/50), papillary mineralization (43/50), hyperplasia of transitional epithelium of the renal pelvis (10/50); ♀: NOAEC; **400 ml/m³**: ♂: body weights in 2nd year ↓; kidneys: tubular hyperplasia (5/20), papillary mineralization (17/20), hyperplasia of the transitional epithelium of the renal pelvis (5/20); ♀: lungs: interstitial fibrosis (28/50), alveolar histiocytosis (29/50) and proteinosis (23/50); pleura: chronic inflammation (27/28); see Section 5.7 for neoplastic findings	
mouse, B6C3F1, 5 ♂, 5 ♀	**17 days**, 0, 25, 50, 100, 200, 400 ml/m³, 6 hours/day, 5 days/week	**50 ml/m³**: NOAEC; **100 ml/m³ and above**: ♂: relative liver weights ↑; ♀: absolute and relative liver weights ↑; **200 ml/m³ and above**: ♂: absolute and relative liver weights ↑	NTP 2005
mouse, CF-1, 100 ♀	**30 days**, 0, 50, 250 ml/m³, 6 hours/day, 5 days/week	**50 ml/m³ and above**: concentration-related irritation of the respiratory tract (loss of cilia of the bronchial epithelium, exudate in the bronchi and alveoli, increased incidence of type 2 pneumocytes in alveolar region); **250 ml/m³**: hepatocytes: vacuolation in the cytoplasm; body weights, organ weights: not specified	MacEwen and Vernot 1978
mouse, C57/BL6, ♂	**20, 28 or 35 days**, 0, 25, 62.5, 125 ml/m³, 22 hours/day, 7 days/week	**up to 125 ml/m³**: body weights, survival and kidney histopathology: no unusual findings	Stone et al. 1987 a
mouse, C57/BL6, 150 ♀	**90 days**, 0, 5, 50 ml/m³, continuous, sacrifice after 90 days (50 animals) or after up to 24 months	**5 ml/m³ and above**: hepatocytes: vacuolation/fatty infiltration (controls: 6%, 5 ml/m³: 87%, 50 ml/m³: 94%); recovery period: thyroid: hyperplasia (controls: 31%, 5 ml/m³: 49%, 50 ml/m³: 56%); lungs: increased presence of crystals and macrophages (controls: 10%, 5 ml/m³: 40%, 50 ml/m³: 38%);	Gaworski et al. 1985

Table 1 (Continued)

Species, strain, number per group	Exposure	Findings	References
		50 ml/m³: recovery period: mammary gland: cysts ↑; thyroid: cysts ↑; pituitary gland: carcinomas (controls: 0%, 5 ml/m³: 4%, 50 ml/m³: 10%); lungs: perivascular inflammation (perivascular cuffing; controls: 10%, 5 ml/m³: 10%, 50 ml/m³: 33%); no kidney changes, no irritation of the respiratory tract	
mouse, B6C3F1, 10 ♂, 10 ♀	**14 weeks**, 0, 25, 50, 100, 200, 400 ml/m³, 6 hours/day, 5 days/week	**25 ml/m³**: NOAEC; **50 ml/m³ and above**: ♂: liver: centrilobular cytomegaly ↑; **100 ml/m³ and above**: liver: relative weights ↑; **200 ml/m³ and above**: liver: absolute and relative weights ↑; **400 ml/m³**: ♂: spermatid counts ↓	NTP 2005
mouse, B6C3F1, 50 ♂, 50 ♀	**105 weeks**, 0, 25, 50, 100, 400 ml/m³, 6 hours/day, 5 days/week	**25 ml/m³**: ♂: NOAEC; ♀: liver: hepatocellular carcinomas (see Section 5.7); **100 ml/m³**: ♂: liver: syncytial alteration ↑ (multinuclear cells; 36/50, controls: 26/50); **400 ml/m³**: ♂: liver: eosinophilic foci ↑ (19/50; controls: 0/50), centrilobular hypertrophy ↑ (36/50; controls: 2/50), necrosis ↑ (19/50; controls: 10/50), syncytial alteration ↑ (multinuclear cells; 44/50; controls: 26/50), erythrophagocytosis ↑ (9/50; controls: 0/50); see Section 5.7 for neoplastic findings	NTP 2005
guinea pigs, Hartley, 25 ♂	**30 days**, 0, 50, 250 ml/m³, 6 hours/day, 5 days/week	**50 ml/m³ and above**: body weights ↓, irritation of the alveoli with multifocal pneumonia not related to the concentration, alveolar wall thickening, exudate (controls: 4%, 50 ml/m³: 36%, 250 ml/m³: 20%); organ weights not specified	MacEwen and Vernot 1978
dogs, beagle, 3 ♂, 3 ♀	**90 days**, 0, 5, 50 ml/m³, continuous	**5 ml/m³ and above**: body weights ↑, blood: serum globulin level ↑ (presumably resulting from an infection); other clinical chemistryl tests, bromsulphthalein retention time (liver function), organ weights and histopathology (37 organs or tissues) unchanged; bronchopneumonia in all animals (including controls), presumably caused by nematode infection; no irritation of the respiratory tract	BUA 2000; Gaworski et al. 1985

AST: aspartate aminotransferase; CPN: chronic progressive nephrosis; LDH: lactate dehydrogenase; LOAEC: lowest observed adverse effect concentration; NOAEC: no observed adverse effect concentration; PCNA: proliferating cell nuclear antigen

Groups of 4 male and 4 female Alderley Park rats were exposed to decahydronaphthalene concentrations of 0 or 1148 mg/m³ (200 ml/m³) by inhalation for 6 hours a day, on 5 days a week, for 20 days. There were no signs of toxicity or any findings after pathological examination of the liver, lungs, spleen, kidneys and adrenal glands. A NOAEC (no observed adverse effect concentration) cannot be derived from the study because of the inadequate documentation (BUA 2000).

In another study, 100 male Sprague Dawley rats, 100 female CF-1 mice and 25 male guinea pigs per group were exposed to decahydronaphthalene concentrations of 0, 287 or 1435 mg/m³ (50 or 250 ml/m³) by inhalation for 6 hours a day, on 5 days a week, for 30 days. Deaths or severe signs of toxicity were not observed in any species. Irritation of the respiratory tract was detected in all species even at the low concentration. Therefore, it was not possible to derive a NOAEC from this study (MacEwen and Vernot 1978). Details of the generation or characterization of the exposure atmosphere were not reported.

Groups of male Fischer rats and male C57BL/6 mice were exposed to decahydronaphthalene concentrations of 0, 25, 62.5 or 125 ml/m³ for 20, 28 or 35 days, for 22 hours a day, on 7 days a week. Female rats were exposed to 125 ml/m³ for 28 days. The body weights and survival were unchanged. Necropsy revealed hyaline droplets in the proximal tubule cells, granular casts in the outer zone of the renal medulla and chronic nephrosis in male rats; the incidence increased with time and the dose. These lesions were not observed in mice (NTP 2005; Stone et al. 1987 a). Thus, a NOAEC was not obtained for male rats, while for female rats and male mice the NOAEC was 125 ml/m³.

In another study, 75 male and 75 female F344 rats and 150 female C57/BL6 mice per group were continuously exposed to decahydronaphthalene concentrations of 0, 5 or 50 ml/m³ for 90 days. Effects on the kidneys were observed in the male rats at the low concentration and above, whereas no changes were observed in the kidneys in the female rats or mice. Mild effects on the liver were observed in mice at 5 ml/m³ and above. See Section 5.7 for the evaluation of the neoplastic changes that occurred (Gaworski et al. 1985).

Groups of 3 male and 3 female beagle dogs were continuously exposed to decahydronaphthalene concentrations of 0, 5 or 50 ml/m³ for 90 days. There were no severe substance-induced effects (Gaworski et al. 1985). All animals had bronchopneumonia that was presumably caused by a nematode infection. It was not possible to derive a NOAEC because the irritative effects could not be evaluated as a result of the respiratory tract infection (BUA 2000).

As part of the NTP programme, inhalation studies were carried out with decahydronaphthalene (purity: > 99%) in male and female F344/N rats and male and female B6C3F1 mice for 2, 14 and 105 weeks. Additional groups of male NBR rats were used concurrently in the 14-day study to investigate the mechanism of nephrotoxicity. This rat strain does not produce α_{2u}-globulin. In the 2-week and 14-week studies, all animals survived until the end of the study, and the body weights were not affected by the treatment. In the 105-week studies, the survival of the exposed animals corresponded to that of the control groups. The body weights

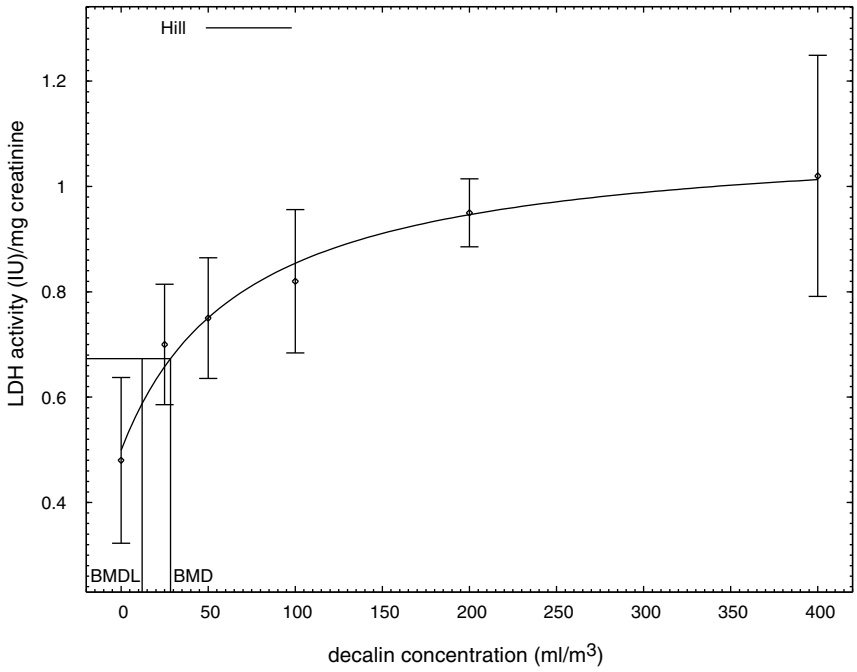


Figure 2 BMD calculation (Hill model with 95% confidence interval) for the end point "increased LDH activity in the urine" in female rats after 14-week exposure to decahydronaphthalene; BMD: 28 ml/m^3; BMDL: 12 ml/m^3

were similar to those of the control groups. In the male rats of the high concentration group, the body weights were slightly reduced in the second year of treatment. Decahydronaphthalene induced α_{2u}-globulin nephropathy in male F344/N rats. In rats and mice of both sexes, exposure to decahydronaphthalene resulted in increased liver weights, but there was no histopathological correlate for this in rats.

In the 14-week study, increased incidences of cytomegaly were observed in male mice at 50 ml/m^3 and above; in the 2-year study, increased incidences of syncytial alteration were found in male mice at 100 ml/m^3 and above and increased incidences of eosinophilic foci, centrilobular hypertrophy, necrosis and erythrophagocytosis in the liver at 400 ml/m^3 and above. The neoplastic findings are described in Section 5.7 (NTP 2005). In mice, the NOAEC was 50 ml/m^3 after 17 days exposure to decahydronaphthalene and 25 ml/m^3 after exposure for 14 weeks. In the 2-year study, 25 ml/m^3 was the NOAEC for males, whereas significantly increased incidences of liver carcinomas were observed at this concentration in female mice. The findings in the kidneys obtained in male F344 rats were induced by α_{2u}-globulin nephropathy and are therefore not taken into consideration in the evaluation (see Section 2). After 16 days exposure, the lowest concentration was the LOAEC (low-

est observed adverse effect concentration) because the liver weights were increased in females at 25 ml/m³ and above. This effect was no longer observed at 25 ml/m³ in the 14-week study. After exposure for 14 weeks, the lowest concentration was likewise the LOAEC because the LDH activity was significantly increased in the urine of the females at 25 ml/m³ and above; the authors attributed this to nephrotoxicity. A benchmark calculation yielded a benchmark dose (BMD) of 28 ml/m³ for the increased LDH activity related to an increase by one standard deviation of the control value with a lower confidence limit (BMDL) of 12 ml/m³. A NOAEC of 100 ml/m³ was derived from the 2-year study. Lung findings were obtained in the females in this study. The elimination of LDH was not investigated.

Conclusions

In male rats, exposure to decahydronaphthalene via inhalation induced α_{2u}-globulin nephropathy, which is not relevant to humans.

The increased LDH activity observed in the urine of female rats in the 14-week inhalation study (NTP 2005) was the most sensitive end point, with a BMDL of 12 ml/m³.

In mice, the NOAEC in the 14-week inhalation study was 25 ml/m³, whereas in the 2-year study, hepatocellular carcinomas were observed in females at 25 ml/m³ (NTP 2005; see also Section 5.7).

Earlier studies described irritation of the respiratory tract at 50 ml/m³ and above after the exposure of rats, mice and guinea pigs to decahydronaphthalene for 30 days (MacEwen and Vernot 1978). These findings were not confirmed in 90-day studies carried out in dogs, rats and mice by the same group of authors (Gaworski et al. 1985) or in inhalation studies of the NTP. Effects on the respiratory tract were observed only in female rats at 400 ml/m³ in the 2-year study (NTP 2005).

5.2.2 Oral administration

In male Sprague Dawley rats given gavage doses of decahydronaphthalene of 200 mg/kg body weight for 3 days, exfoliated tubule epithelial cells were found in the renal tubules. There were no inflammatory infiltrates in the tubular epithelium (NTP 2005).

Groups of 10 male and 20 female F344 rats were given gavage doses of decahydronaphthalene (purity: > 98%) once a day for 5 or 12 days. In male rats the doses were 0, 100, 500, 1000 or 2000 mg/kg body weight and day and in female rats 0, 1000, 1500, 1750 or 2000 mg/kg body weight and day. Afterwards, only the kidneys were examined histopathologically. The males of the high dose group had either died or were sacrificed because of severe toxicity on day 6 of the study. Clinical signs included reddish-brown discoloration around the anus, mouth, nostrils and eyes, reduced reaction and dehydration. By the end of the study, 5 females of the high dose group had died. Also in the middle dose groups, 1 female died. The clinical signs observed in these animals corresponded to those in males. Histo-

pathological changes in the kidneys were found only in male rats. In male control animals, hyaline droplets were observed in small amounts in the tubule epithelial cells of less than 1% of the tubules. In exposed animals, the hyaline droplets were considerably larger than in control animals. After exposure for 12 days, granular casts were found in the male rats in the outer zone of the renal medulla at 1000 mg/kg body weight (Stone et al. 1987 b).

Groups of 7 male and 9 female F344 rats were given undiluted *cis-decalin* or *trans-decalin* (purity: > 99%) by gavage every second day for 14 days. The doses administered at each treatment were 2500 mg/kg body weight in males and 3000 mg/kg body weight in females; the control animals were given water. The histopathological examination of the kidneys from the males revealed the accumulation of hyaline droplets in the proximal tubule cells and multifocal casts of necrotic cells and debris in the tubules close to the corticomedullary transitional zone. The females were not found to have any kidney damage (Olson et al. 1986).

Oral administration of decahydronaphthalene in doses of 150 mg/kg body weight and day for 14 days caused the accumulation of α_{2u}-globulin in the kidneys of male Sprague Dawley rats (NTP 2005).

Male F344 rats were given oral decahydronaphthalene doses of 0, 75, 150 or 300 mg/kg body weight and day on 5 days a week, for 5 or 26 days. The animals were sacrificed 24 hours after the last treatment. Signs of toxicity were not observed during the treatment. The relative liver and kidney weights were significantly increased after 6 and 27 days at the high dose, and the relative liver weights were significantly increased after 27 days in the group given 150 mg/kg. As no histopathological changes were found in the liver, the increased liver weights were considered to be the result of the induction of mixed-function oxidases. The dose-dependent formation of hyaline droplets in the kidneys was most pronounced after 6 days. Signs of chronic nephrosis with the formation of casts in the region of the outer medulla were observed after 27 days in the high dose group. Because of an error during the study, no data are available for the two lower doses (BUA 2000).

Groups of 30 male and 5 female rats were given gavage doses of decahydronaphthalene of 0, 10, 100 or 1000 mg/kg body weight and day for 28 days. On days 1, 3, 7, 14 and 28, 5 males from each group were sacrificed and on day 28, all the females were sacrificed. Another 5 males per group were observed for 14 days. The formation of hyaline droplets was detected in the proximal tubule cells of the kidneys of the males at 100 mg/kg body weight and above; this increased with the dose and time. An increased incidence of granular casts was found in the kidneys of the animals that were observed after treatment. Examination by light and electron microscope did not reveal any changes in the kidneys of female rats. In female rats, a NOAEL (no observed adverse effect level) of 1000 mg/kg body weight and day for kidney changes was derived from this study (BUA 2000; ECHA 2013).

5.2.3 Dermal application

There are no data available.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

Undiluted decahydronaphthalene (0.5 ml; purity: 99%) was applied semi-occlusively to the shaved dorsal skin of rabbits for 4 hours. The treatment induced severe irritation of the skin (irritation index: 7.5/8) and necrosis. Necrosis was not observed after 3-minute non-occlusive exposure or 1-hour semi-occlusive exposure to decahydronaphthalene. After 4-hour exposure, the means of the scores recorded after 24, 48 and 72 hours were 4/4 for erythema and 3.33/4 for oedema. The changes were not reversible within 14 days; therefore, undiluted decahydronaphthalene was corrosive to the rabbit skin (BUA 2000; ECHA 2013).

In a test using Teflon test chambers (area: 6 cm^2), amounts of 0.5 ml diluted decahydronaphthalene (5%, 10%, 25% and 50% w/w in almond oil) were applied to the shaved rabbit skin for 4 hours. The skin was then rinsed with water and the erythema was evaluated after 1, 24, 48 and 72 hours. The maximum concentration at which the mean score for erythema was not higher than 2 on a scale up to 4 was 25%. Diluted decahydronaphthalene caused irritation of the rabbit skin (Jacobs et al. 1987).

In a maximization test in guinea pigs (see Section 5.4), 24-hour occlusive treatment with 20% decahydronaphthalene in corn oil did not cause irritation of the skin (BUA 2000; ECHA 2013).

5.3.2 Eyes

In a study according to OECD Test Guideline 405, the application of 0.1 ml undiluted decahydronaphthalene did not cause irritation of the cornea or iris; the marked redness and oedema of the conjunctivae that were observed subsided completely after 6 and 8 days. The means of the scores recorded after 24, 48 and 72 hours were 0/4, 0/2, 0.78/3 and 0.44/4 for the cornea, iris, and redness and chemosis of the conjunctivae, respectively. The irritation index was 3.5 of 110. Therefore, decahydronaphthalene was not found to cause irritation of the rabbit eye (BUA 2000; ECHA 2013).

5.4 Allergenic effects

In a maximization test carried out in 20 female guinea pigs according to OECD Test Guideline 406, decahydronaphthalene (induction treatment: 5% intradermal

and 60% topical application; challenge treatment: 20% topical application) did not cause sensitization (BUA 2000; ECHA 2013).

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

At the end of the 14-week inhalation studies carried out as part of the NTP programme, reproductive parameters were examined in male and female rats and mice (see Section 5.2.1; NTP 2005). No changes in the spermatid count or sperm motility were observed in male F344 rats. In male B6C3F1 mice, the trend test revealed a concentration-dependent reduction in the number of spermatids in the testes; this decrease was significant in the high concentration group (400 ml/m^3). The testis weights were unchanged. The oestrus cycle was not significantly changed in female F344 rats or female B6C3F1 mice (NTP 2005). The NOAEC for effects on reproductive parameters was 400 ml/m^3 for rats and female mice and 100 ml/m^3 for male mice.

5.5.2 Developmental toxicity

In a study, 48 CD-1 mice were given daily gavage doses of decahydronaphthalene of 2700 mg/kg body weight from days 6 to 13 of gestation. A total of 7 dams died (no other details), body weight gains were significantly increased and the number of viable pups was unchanged. Changes in birth weights and body weight gains or in the number of live pups per litter and their survival were not observed in the offspring up to day 3 of life. Malformations were not investigated. This screening study did not reveal evidence of an embryotoxic potential for decahydronaphthalene. However, teratogenicity was not examined (Hardin et al. 1987).

5.6 Genotoxicity

5.6.1 In vitro

A Salmonella mutagenicity test with the strains TA98, TA100, TA1535, TA1537 and TA1538 did not reveal mutagenicity at decahydronaphthalene concentrations of up to 10 000 µg/plate either with or without metabolic activation (BUA 2000).

In another Salmonella mutagenicity test with and without pre-incubation, decahydronaphthalene was not mutagenic in the presence or absence of metabolic activation (Aroclor-induced liver microsomes) up to the highest concentration tested of 5000 µg/plate in the strains TA98, TA100, TA1535, TA1537 and TA1538 (BUA 2000).

Negative results were likewise obtained in a Salmonella mutagenicity test carried out as part of the NTP programme with the strains TA97, TA98, TA100 and TA1535 in a concentration range of 1 to 10 000 µg/plate in the presence and absence of metabolic activation (Aroclor-induced S9 mix of rats and hamsters) (NTP 2005).

Decahydronaphthalene yielded negative results in an in vitro chromosomal aberration test with CHL cells (a cell line derived from Chinese hamster liver) at concentrations of 0.63 to 5.0 mg/ml with metabolic activation (rat liver S9 mix) and at concentrations of 0.15 to 1.2 mg/ml without metabolic activation. Cytotoxicity was observed at 0.63 mg/ml and above without metabolic activation. The concurrent positive controls induced the expected result (Miura et al. 1993).

In a mouse lymphoma test with L5178Y cells, negative results were likewise obtained with decahydronaphthalene at concentrations of 9 to 61 µg/ml without metabolic activation and at 250 to 450 µg/ml with metabolic activation. Cytotoxicity was observed with and without metabolic activation at 300 and 48 µg/ml and above, respectively (BUA 2000; ECHA 2013).

5.6.2 In vivo

After 8-week and 12-week continuous inhalation exposure to decahydronaphthalene concentrations of 5 or 50 ml/m^3 (28.7 or 287 mg/m^3), no significant increase in sister chromatid exchange or the incidence of micronuclei was observed in the peripheral lymphocytes of beagle dogs. Concurrent positive controls were not used; the method and the description of the results do not meet present-day requirements (Benz et al. 1979).

An in vivo micronucleus test was carried out as part of the NTP programme in male and female B6C3F1 mice after inhalation exposure for 3 months to decahydronaphthalene concentrations of 0, 25, 50, 100, 200 or 400 ml/m^3. The number of polychromatic erythrocytes was slightly increased in both sexes at high concentrations. No increase in the number of micronuclei was detected in the peripheral normochromatic erythrocytes of female mice compared with the incidence in the controls. The incidence of micronuclei was slightly increased in the males. This result was statistically significant in the trend test, but not in the pairwise comparison. A positive control was not included (NTP 2005).

Conclusions

Decahydronaphthalene was unequivocally found not to be genotoxic in vitro in tests for gene mutations in bacteria and mammalian cells and in chromosomal aberration tests. In a valid in vivo micronucleus test, the incidence of micronuclei was slightly increased in male mice, and there was a statistically significant increase in the trend test, but not in the pairwise comparison. In female mice, decahydronaphthalene did not induce micronuclei. Overall, the data are not sufficient to substantiate the suspected genotoxicity as this positive in vivo finding was an isolated

result that is not supported by corresponding in vitro data or by mechanistic data. Therefore, the Commission does not consider decahydronaphthalene to be genotoxic.

5.7 Carcinogenicity

5.7.1 Short-term studies

In a dermal carcinogenicity study with benzo[*a*]pyrene in C3H/He mice, decahydronaphthalene and *n*-dodecane were used as a solvent mixture (50:50 w/w). An amount of 50 mg of the mixture was applied to the skin of 50 control animals three times a week for 50 weeks. None of the 30 animals that survived to the end of the exposure period developed tumours. There are no data available for pure decahydronaphthalene (BUA 2000).

5.7.2 Long-term studies

Evidence of neoplastic changes in rats and mice was found in the 90-day studies with lifelong observation described in Section 5.2.1. A slightly increased incidence of uterine adenocarcinomas in female rats and evidence of hepatocellular neoplasms in mice were reported without any further details. Because of the incomplete documentation, these data cannot be included in the evaluation of the carcinogenicity of decahydronaphthalene. In addition, a significant, but not dose-related increase in pituitary adenomas in male rats and a significant, dose-related increase in pituitary carcinomas in female mice were reported. These findings are, however, relativized by the unusually low incidence of pituitary tumours in the concurrent control groups compared with that in the historical controls. Therefore, the relevance of these findings remains unclear (BUA 2000; Gaworski et al. 1985).

As part of the NTP programme, 105-week inhalation studies were carried out with decahydronaphthalene (purity: > 99%) in male and female F344/N rats and male and female B6C3F1 mice (see Table 2). The combined incidences of tubular adenomas and carcinomas of the kidneys were significantly increased in the male rats. However, the finding is relativized by the simultaneous occurrence of α_{2u}-globulin nephropathy. In addition, the combined incidences of benign and malignant adrenal phaeochromocytomas were significantly increased in the male rats at concentrations of 100 and 400 ml/m^3. There was a significant relationship between the severity of nephropathy and the incidence of phaeochromocytomas. The high mortality of 54% to 60% in the males of the 3 low treatment groups limits the validity of this study. Significantly increased incidences of hepatocellular carcinomas and adenomas were observed in the female mice at 25 and 400 ml/m^3, respectively. In addition, there was a positive trend for the incidences of uterine polyps alone and combined with uterine sarcomas, but the incidences were not or only slightly above those in the historical controls (NTP 2005).

Table 2 Studies of the carcinogenicity of decahydronaphthalene after inhalation exposure

Author:	NTP 2005
Substance:	decahydronaphthalene (> 99% pure)
Species:	**rat**, F344/N, 50 ♂, 50 ♀
Administration route:	inhalation
Concentration:	0, 25, 50 (only ♂), 100, 400 ml/m^3
Duration:	105 weeks, 5 days/week, 6 hours/day
Toxicity:	25 ml/m^3 and above: ♂: kidneys: accumulation of hyaline droplets, tubular hyperplasia, mineralization of the papilla, hyperplasia of the transitional epithelium of the renal pelvis; 400 ml/m^3: ♂: body weights in 2nd year ↓; ♀: lungs: interstitial fibrosis, alveolar histiocytosis and proteinosis; pleura: chronic inflammation (see also Section 5.2.1)

		exposure concentration (mg/m^3)				
		0	25	50	100	400
survival	♂	28/50 (56%)	23/50 (46%)	23/49 (47%)	20/50 (40%)	14/20 (70%)
	♀	32/50 (64%)	35/50 (70%)	–	39/50 (78%)	28/50 (56%)
tumours and pre-neoplasms						
kidneys:						
tubular hyperplasia	♂	0/50[a)]	11/50 (22%)**	11/49 (22%)**	15/50 (30%)**	5/20 (25%)**
	♀	1/50 (2%)[a)]	4/46 (9%)	–	4/49 (9%)	2/50 (4%)
tubular adenomas	♂	1/50 (2%)[a), c)] 2.4%[b)]	2/50 (4%) 4.9%	6/49 (12%) 14.0%	9/50 (18%)** 21.8%	5/20 (25%)** 26.7%
		poly-3 trend test: P = 0.005				
	♀	0/50[a)]	0/50	–	0/50	0/50
tubular adenomas and carcinomas	♂	1/50 (2%)[a), c)] 2.4%[b)]	3/50 (6%) 7.3%	7/49 (14%)* 16.3%	12/50 (24%)*** 28.9%	6/20 (30%)*** 31.8%
		poly-3 trend test: P = 0.002				
	♀	0/50[a)]	0/50	–	0/50	0/50
adrenal medulla						
benign phaeochromocytomas	♂	7/49 (14%)[a), d)] 16.7%[b)]	9/49 (18%) 22.0%	11/49 (22%) 25.0%	10/49 (20%) 24.8%	6/20 (30%) 31.8%
		poly-3 trend test: P = 0.173				
malignant phaeochromocytomas	♂	2/49 (4%)[a), e)] 4.8%[b)]	0/49 (0%) 0.0%	2/49 (4%) 4.6%	7/49 (14%) 17.3%	3/20 (15%) 16.0%
		poly-3 trend test: P = 0.034				

Table 2 (Continued)

benign and malignant phaeochromocytomas	♂	8/49 (16%)[a), f)] 19.1%[b)]	9/49 (18%) 22.0%	13/49 (27%) 29.2%	16/49 (33%)* 38.6%	8/20 (40%)* 42.2%
		poly-3 trend test: P = 0.038				
	♀	1/50 (2%)[a)]	3/48 (6%)	–	4/49 (8%)	1/49 (2%)

*p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001 (poly-3 test)
[a)] overall number (number of animals with neoplasms per number of examined animals)
[b)] adjusted incidence (incidence of neoplasms estimated in poly-3 trend test after correction for intercurrent mortality)
historical controls, incidence, mean ± standard deviation and range (NTP 2005):
[c)] 3/906; 0.4 ± 0.9%; 0–2%
[d)] 100/903; 10.8 ± 5.8%; 3–24%
[e)] 18/903; 2.3 ± 2.7%; 0–11%
[f)] 116/903; 12.8 ± 5.9%; 5–27%

Author:	NTP 2005
Substance:	decahydronaphthalene (> 99% pure)
Species:	**mouse**, B6C3F1, 50 ♂, 50 ♀
Administration route:	inhalation
Concentration:	0, 25, 100, 400 ml/m³
Duration:	105 weeks, 5 days/week, 6 hours/day
Toxicity:	100 ml/m³: ♂: liver: syncytial alteration ↑ (multinuclear cells); 400 ml/m³: ♂: liver: eosinophilic foci ↑, centrilobular hypertrophy ↑, necrosis ↑, syncytial alteration ↑, erythrophagocytosis ↑ (see also Section 5.2.1)

		exposure concentration (ml/m³)			
		0	25	100	400
survival	♂	40/50 (80%)	41/50 (82%)	36/50 (72%)	34/50 (68%)
	♀	37/49 (76%)	28/50 (56%)	35/50 (70%)	36/50 (72%)
tumours and pre-neoplasms					
liver:					
hepatocellular adenomas	♂	22/50 (44%)[a)]	22/50 (44%)	14/50 (28%)	27/20 (54%)
		poly-3 trend test: not specified			
	♀	7/49 (14%)[a), c)] 15.6%[b)]	13/50 (26%) 29.7%	8/50 (16%) 17.6%	17/50 (34%)* 37.2%
		poly-3 trend test: P = 0.024			
hepatocellular carcinomas	♂	10/50 (20%)[a)]	7/50 (14%)	10/50 (20%)	11/50 (22%)
		poly-3 trend test: not specified			
	♀	4/49 (8%)[a), d)] 8.9%[b)]	16/50 (32%)** 35.5%	6/50 (12%) 13.1%	5/50 (10%) 10.9%
		poly-3 trend test: P = 0.115 (negative trend)			

Table 2 (Continued)

hepatocellular adenomas and carcinomas	♂	28/50 (56%)[a), e)] 57.5%[b)]	26/50 (52%) 53.7%	22/50 (44%) 44.9%	34/50 (68%) 72.2%
		poly-3 trend test: P = 0.026			
	♀	11/49 (22%)[a), f)] 24.5%[b)]	27/50 (54%)*** 58.4%	14/50 (28%) 30.3%	20/50 (40%)* 43.5%
		poly-3 trend test: P = 0.339			
uterus					
polyps	♀	0/49 (0%)[a), g)] 0.0%[b)]	0/50 (0%) 0.0%	2/50 (4%) 4.4%	3/50 (6%) 6.6%
		poly-3 trend test: P = 0.049			
polyps and sarcomas	♀	0/49 (0%)[a), g)] 0.0%[b)]	0/50 (0%) 0.0%	2/50 (4%) 4.4%	4/50 (8%) 8.8%
		poly-3 trend test: P = 0.013			

*p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001 (poly-3 test)
[a)] overall number (number of animals with neoplasms per number of examined animals)
[b)] adjusted incidence (incidence of neoplasms estimated in the poly-3 trend test after correction for intercurrent mortality)historical controls, incidence, mean ± standard deviation and range (NTP 2005):
[c)] 144/954; 15.9 ± 6.1%; 7–28%
[d)] 69/954; 7.8 ± 4.4%; 3–16%
[e)] 441/959; 48.4 ± 12.9%; 26–72%
[f)] 203/954; 22.6 ± 9.1%; 9–40%
[g)] 15/959; 1.6 ± 2.2%; 0–6%

Conclusions

In male F344/N rats and female B6C3F1 mice, exposure to decahydronaphthalene induced the species-specific kidney tumours and a high incidence of spontaneous tumours in the liver, respectively. In addition, pituitary tumours were observed, but their relevance is relativized by the very low control incidence in the study. There was also a positive trend for uterine polyps in combination with uterine sarcomas, but the incidences were not or only slightly above those in the historical controls. The increased incidences of phaeochromocytomas in male rats were caused by a disturbance in calcium homoeostasis induced by nephrotoxicity (Greim et al. 2009).

6 Manifesto (MAK value/classification)

Nephrotoxicity is the critical effect of decahydronaphthalene.

MAK value. Data from humans suitable for deriving a MAK value are not available.

The α_{2u}-globulin nephropathy observed in male rats after exposure to decahydronaphthalene is species and sex-specific and is therefore not taken into account in the evaluation.

The most sensitive end point was the increased LDH activity in the urine of female rats in the 14-week inhalation study. As no histopathological changes were detected in the 2-year study in the kidneys of female rats at considerably higher concentrations, the LDH activity in the urine is a very sensitive parameter, and an increase in the effects with the exposure period is not expected. A benchmark calculation yielded a benchmark dose (BMD) of 28 ml/m^3 for the increased LDH activity related to an increase by one standard deviation of the control value with a lower confidence limit (BMDL) of 12 ml/m^3. As this value was obtained from animal studies, a MAK value of 5 ml/m^3 can be derived according to the procedure of the Commission (see Section I of the List of MAK and BAT Values). Decahydronaphthalene was corrosive to the skin, whereas no irritation was observed in the eyes. In the NTP inhalation studies, effects on the respiratory tract were found only in female rats and only at 400 ml/m^3 and above. Therefore, no irritation is expected to occur after exposure at the level of the MAK value.

Peak limitation. As the MAK value is derived from a systemic effect, decahydronaphthalene is classified in Peak Limitation Category II. In the target organ, the kidneys of female rats, its half-life is about 1 to 2 hours (estimated from a graph, NTP 2005). According to the procedure of the Commission (see documentation "Spitzenbegrenzung" 2011, available in German only), this results in an excursion factor of 2.

Prenatal toxicity. No toxic effects on development were detected in the offspring of female mice treated with decahydronaphthalene by gavage up to day 3 of life. Teratogenicity was not investigated in this screening study. No other studies of the toxic effects on prenatal development were carried out. Therefore, decahydronaphthalene has been classified in Pregnancy Risk Group D.

Carcinogenicity. Decahydronaphthalene is not regarded to be genotoxic. The kidney neoplasms observed in male rats after exposure to decahydronaphthalene were caused by α_{2u}-globulin nephropathy. This species and sex-specific finding was not included in the evaluation of the carcinogenic effects. The increased incidences of phaeochromocytomas in male rats were caused by a disturbance in calcium homoeostasis induced by nephrotoxicity (Greim et al. 2009). Moreover, the benign phaeochromocytomas, which are regarded as precursors, were not significantly increased. This relativizes the relevance of the significant increase in malignant phaeochromocytomas in the trend test. In mice, the incidences of uterine polyps and sarcomas were significantly increased in the trend test, but were not or only slightly above the range in the historical controls. In female mice, the incidence of hepatocellular adenomas was increased only at 400 ml/m^3 and that of hepatocellular carcinomas only at 25 ml/m^3. The incidences of 34% and 32% were

above the historical control values of 7% to 28% and 3% to 16%, respectively. However, the incidence of hepatocellular carcinomas was not related to the concentration and the incidences observed at the higher concentrations were in the range of those in the control groups. No liver tumours were found in male mice. Although pituitary tumours developed in male rats and female mice, their relevance is relativized by the very low incidence in the study compared with that in the historical controls.
Decahydronaphthalene is therefore not classified in any of the carcinogen categories.

Germ cell mutagenicity. Negative results were obtained in all available in vitro tests (bacterial mutation tests, chromosomal aberration tests and mouse lymphoma tests). A micronucleus test in mice, which is the only valid in vivo test (NTP 2005), yielded negative results in females after inhalation exposure to decahydronaphthalene concentrations of up to 400 ml/m^3 for 3 months. In males, there was only a slight increase in the incidence of micronuclei in peripheral normochromatic erythrocytes, whereas this increase was significant in the trend test, but not in the pairwise comparison. However, these data are not sufficient to substantiate suspected germ cell mutagenicity as this positive in vivo finding was an isolated result that is not supported by either corresponding in vitro data or by mechanistic data. Decahydronaphthalene is therefore not classified in any of the germ cell mutagen categories.

Absorption through the skin. There are no studies available in animals or humans of the absorption of decahydronaphthalene through the skin. The dermal LD_{50} is higher than 5000 mg/kg body weight. Using the models of Fiserova-Bergerova et al. (1990), Guy and Potts (1993) and Wilschut et al. (1995), absorbed amounts of 49.9, 0.703 and 0.234 mg were calculated under standard conditions.

The MAK value is derived from a systemic effect and is 29 mg/m^3. Assuming 100% absorption by inhalation, 8-hour exposure and a respiratory volume of 10 m^3, 290 mg is expected to be absorbed. Therefore, the calculated amount absorbed through the skin, assuming worst-case conditions, is less than 25% of the systemic NOAEL. Also, decahydronaphthalene has a relatively high vapour pressure, which in addition minimizes absorption of the substance through the skin. Prolonged, unnoticed contact with highly concentrated solutions of decahydronaphthalene is unlikely because of its severely irritating effects on the skin. Therefore, decahydronaphthalene is not designated with an "H" (for substances which can be absorbed through the skin).

Sensitization. There are no clinical findings that would substantiate sensitizing effects of decahydronaphthalene on the skin or respiratory tract. A maximization test carried out according to the guidelines yielded negative results. Decahydro-

naphthalene is therefore not designated with either “Sa” or “Sh” (for substances which cause sensitization of the airways or skin).

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completed 26.02.2014