Pentane (all Isomers)

MAK value (2004)	**1000 ml/m³ (ppm) ≙ 3000 mg/m³**
Peak limitation (2002)	**Category II, excursion factor 2**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2004)	**Pregnancy Risk Group D**
Germ cell mutagenicity	**–**
BAT value (2004)	**–**
Synonyms	pentane
Chemical name (CAS):	
CAS number	109-66-0
	n-pentane
	78-78-4 *iso*-pentane
	463-82-1 *t ert*-pentane
Structural formula	$CH_3–(CH_2)_3–CH_3$
	$(H_3C)_2CH–CH_2–CH_3$
	$C(CH_3)_4$
Molecular formula	C_5H_{12}
Molecular weight	72.15
Melting point	–129.7°C *n*-pentane (HSDB 2004)
	–159.9°C *iso*-pentane (HSDB 2004)
	–16.6°C *tert*-pentane (HSDB 2004)
Boiling point	36.1°C *n*-pentane (HSDB 2004)
	27.8°C *iso*-pentane (HSDB 2004)
	9.5°C *tert*-pentane (HSDB 2004)
Vapour pressure (at 25°C)	685 h Pa *n*-pentane (HSDB 2004)

The MAK-Collection Part I, MAK Value Documentations 2015
DFG, Deutsche Forschungsgemeinschaft

(at 21.1°C)	793 hPa *iso*-pentane (HSDB 2004)
(at 25°C)	1719 hPa *tert*-pentane (HSDB 2004)
log K_{OW}[1)]	3.39 *n*-pentane (HSDB 2004)
	2.30 *iso*-pentane (HSDB 2004)
	3.11 *tert*-pentane (HSDB 2004)
1 ml/m³ (ppm) ≙ 2.99 mg/m³	**1 mg/m³ ≙ 0.33 ml/m³ (ppm)**

The MAK value of 1000 ml/m³ (3000 mg/m³) which was established in 1958 in accordance with the TLV value valid at the time. The present documentation is based mainly on the reviews of toxicological data for pentane (ACGIH 2001; OECD 2001).

1 Toxic Effects and Mode of Action

The toxic effects and mode of action of *iso*-pentane and *tert*-pentane are similar to those of *n*-pentane. In a study of *n*-pentane (purity 99%) applied semi-occlusively to the skin of volunteers for 24 hours, *n*-pentane was determined to be clinically not irritating. On the other hand, in an earlier study in volunteers with undiluted pentane (isomeric form not specified; purity unclear), burning on the skin was reported, and after the application of the substance for five hours pronounced irritation and the formation of blisters was observed. The isomers are absorbed by inhalation. In experiments with animals, the acute toxicity was found to be low. Exposure to high *n*-pentane concentrations in the range of 30 000 to over 100 000 ml/m³ led to effects of increasing severity from anaesthesia to narcosis and respiratory arrest. No effects were seen in rats after exposure to *n*-pentane concentrations of 20 000 mg/m³ (6600 ml/m³) for up to 90 days. No irritating or sensitizing effects occurred in experiments with animals. *n*-Pentane yielded negative results in tests with *Salmonella typhimurium* strains. In a test for chromosomal aberrations in CHO cells, a questionably positive result was obtained in a repeated test series. In the rat, *n*-pentane was not found to be genotoxic in micronucleus tests. Also *iso*-pentane was not mutagenic in tests with *Salmonella typhimurium*. No toxic effects on reproduction were found for *n*-pentane up to 10 000 ml/m³ or 1000 mg/kg body weight. No data are available for the carcinogenicity of the three isomers.

---

1) *n*-octanol/water partition coefficient

2 Mechanism of Action

On the basis of a regression analysis of the LC_{50} data in relation torelevant partition parameters and the inclusion of pharmacokinetic data, Hau et al. (1999) concluded that the mechanism of lethal toxicity in alcohols and alkanes is probably the result of a non-specific biophysical reaction of the substance with the lipid membranes.

3 Toxicokinetics and Metabolism

The solubility of *n*-pentane in human blood is low (Perbellini et al. 1985). After inhalation, the pentane isomers in humans and animals are rapidly metabolized step by step to form CO_2 (Van Rij and Wade 1987). In rat liver microsomes, *n*-pentane was oxidized in vitro to 2-pentanol and 3-pentanol, and *iso*-pentane to 2-methyl-2-butanol, 3-methyl-2-butanol, 2-methyl-1-butanol and 3-methyl-1-butanol. *tert*-Pentane is hydroxylated to 2,2-dimethylpropanol in rat liver microsomes (Frommer et al. 1970). After male F344 rats were exposed for 50 to 70 minutes via inhalation to *n*-pentane, *iso*-pentane and *tert*-pentane, respectively 19.0%, 8.6% and 5.4%, of the dose was absorbed by the lungs. An association was observed between the lower toxicity of the branched compounds and the lower percentage absorbed of these compounds after inhalation (API 1987; Galvin and Marashi 1999 a, b; Galvin and Panson 1999). The API study (1987) bears the note that it was taken out of the API publication series. The authors state that the results could be out of date. No serious deficiencies could be found after a review of the study, however. Pentane penetrates the excised rat skin (Tsuruta 1982).

For an aqueous solution saturated with *n*-pentane, a dermal flux of 0.337 mg/$cm^{-2} \times h^{-1}$ is obtained in the model of Fiserova-Bergerova et al. (1990) and of 0.007 mg/$cm^{-2} \times h^{-1}$ in that of Guy and Potts (1993). For the exposure of both hands and forearms (about 2000 cm^2), this corresponds to the absorption of 673 mg or 14 mg.

The elimination of *n*-pentane in rats occurs with a half-time of 7.8 minutes. After *n*-pentane concentrations of more than 100 ml/m^3, saturation was observed during the course of elimination (Filser et al. 1983). After the exposure of rats to a mixture of radioactively labelled and unlabelled *n*-pentane via inhalation for 8 hours, 50% was exhaled as radioactive CO_2. Of the total radioactivity, 7.6% was recovered in the urine, 6.9% in the muscles, 3.4% in the liver and 2.2% in the small intestine. The values found in the kidneys, lungs, testes, brain, heart, large intestine, spleen and fat were in the range between 0.12% and 0.52%. The percentage of total radioactivity found in tissue was given as 14.9%. A further 2% was found in the blood (Daugherty et al. 1988).

n-Pentane can be generated in vivo during the peroxidative degradation of unsaturated fatty acids. The endogenous production of *n*-pentane was 8.1 nmol/h and

kg body weight (585 ng/h and kg body weight) in rats, and 0.11 nmol/h and kg body weight (8 ng/h and kg body weight) in humans (Filser et al. 1996).

4 Effects in Humans

4.1 Single exposures

Short-term inhalation exposure for 10 minutes to 5000 ml/m^2 of a mixture consisting of 76.5% *n*-pentane, 20.8% *iso*-pentane, 1.4% hexane and 1.3% butane did not produce any impairment of health in volunteers (no other details) (ACGIH 2001).

4.2 Repeated exposure

Five cases of neuropathy were reported among the employees of a company that produced leather belts (Gaultier et al. 1973). The neuropathy was associated with the solvent mixture consisting of 80% pentane (no details of isomers), 14% heptane and 5% hexane. In three cases, loss of appetite, weakness, paraesthesia, fatigue and bilateral muscle failure mainly in the feet were observed. Electromyographic measurements (recording the bioelectric activity of the muscles in the form of an electromyogram, as a rule by inserting needle electrodes) and determination of the nerve conduction velocity confirmed damage to the peripheral nerves (Gaultier et al. 1973; ACGIH 2001;).

Polyneuropathy was diagnosed in four persons after exposure for between 5 months and 7 years to a mixture consisting of 3% benzene, 3% toluene, 7.5% octane, 10% heptane, 12.5% *n*-hexane, 13% *n*-pentane and 51% unknown components. The authors suspect that *n*-hexane caused the polyneuropathy (Takeuchi et al. 1975).

4.3 Local effects on skin and mucous membranes

Undiluted pentane (isomeric form not specified; purity unclear) was applied to the skin using open glass rods. The volunteers reported persistent burning on the skin, accompanied by stinging. Pronounced irritation with blister formation was observed after exposure for five hours. A narcotic effect was not reported by the volunteers (Oettel 1936).

2.0 ml undiluted *n*-pentane (purity > 95%) was applied directly to the skin of 15 volunteers. After 15 minutes, the site of application was covered with a semipermeable surgical dressing for 24 hours. According to the study protocol, the skin was investigated 30 minutes and 24 hours after the removal of the dressing. The publi-

cation does not mention the results found after 30 minutes. After 24 hours, erythema with a Draize score of 1 was reported in 4 volunteers; the average score was 0.27 (maximum score: 4). There were no findings in the other volunteers. *n*-Pentane was regarded as clinically not irritating by the authors (McKee et al. 1998).

4.4 Allergenic effects

There are no data available for the allergenic effects of the pentane isomers.

4.5 Reproductive toxicity

There are no data available for the toxic effects on reproduction of the pentane isomers.

4.6 Genotoxicity

There are no data available for the genotoxicity of the pentane isomers.

4.7 Carcinogenicity

There are no data available for the carcinogenicity of the pentane isomers.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

After single exposures, the toxicity of the pentane isomers is low. The 4-hour LC_{50} for *n*-pentane in rats was higher than 6106 ml/m^3 (18 260 mg/m^3) (Galvin and Marashi 1999 a). Fühner (1921) reported that the inhalation of *n*-pentane concentrations of 270 000 mg/m^3 did not have narcotic effects in the mouse, while 380 000 mg/m^3 caused narcosis with a possibly lethal effect. Exposure to *n*-pentane concentrations of 130 000 ml/m^3 (388 700 mg/m^3) for 30 minutes was lethal for mice (ACGIH 2001). Mice were narcotized after 5 to 60 minutes exposure to *n*-pentane concentrations of 90 000 to 120 000 ml/m^3 (269 100–358 800 mg/m^3)

(Galvin and Marashi 1999 a). Groups of 4 Swiss mice were exposed to *n*-pentane concentrations of 1000, 2000, 4000, 8000, 16 000, 32 000, 64 000 and 128 000 ml/m^3 (2990, 5980, 11 960, 23 920, 47 840, 95 680, 191 360 and 382 720 mg/m^3) in an exposure chamber for 5 minutes, and the effect of the exposure on the respiratory tract of each mouse was recorded using a plethysmograph (a device for measuring and recording changes in lung volume; the course of the curve can provide information on narcotic and irritating effects of a compound after inhalation). An anaesthetizing effect and irritation of the respiratory tract in mice were observed after 5 minutes exposure to *n*-pentane concentrations of 32 000 to 64 000 ml/m^3; there were no anaesthetic effects after exposure to *n*-pentane concentrations of 16 000 ml/m^3. The animals were narcotized at 128 000 ml/m^3 (Swann et al. 1974). After repeated exposure of male CD-1 mice to *n*-pentane concentrations of 5559 ml/m^3 (16 620 mg/m^3) for one minute, no irritation in the upper respiratory tract was observed (Galvin and Marashi 1999 a).

In 6 mice, slight narcosis was observed after 10 minutes exposure to *n*-pentane concentrations of 70 000 ml/m^3 (209 300 mg/m^3) and after 1.3 minutes exposure to 90 000 ml/m^3 (269 100 mg/m^3) (Stoughton and Lamson 1936). Five of 11 animals died after exposure for 2 hours to *n*-pentane concentrations of 100 000 ml/m^3 (299 000 mg/m^3), and 9 of 10 animals after exposure to 110 000 ml/m^3 (328 900 mg/m^3). Slight narcosis was observed after 11.6 minutes in 6 mice after exposure to *iso*-pentane concentrations of 90 000 ml/m^3 and after 30 minutes in 5 mice after exposure to *tert*-pentane concentrations of 20 000 ml/m^3 (59 800 mg/m^3). Two of 10 mice died after exposure for 2 hours to *iso*-pentane concentrations of 13 000 ml/m^3 (38 870 mg/m^3), and 2 of 5 mice after exposure to *tert*-pentane concentrations of 340 000 ml/m^3 (1 016 600 mg/m^3). The reaction of mice to milk within a fixed period of time after the inhalation of *n*-alkanes such as *n*-pentane was used to obtain information about the reaction behaviour of exposed animals. After the inhalation of *n*-pentane concentrations of 36 130 ml/m^3 (108 030 mg/m^3) for 30 minutes, the mice no longer reacted within 60 seconds to the milk offered them (Glowa 1991).

An LC_{50} of 422 730 ml/m^3 (1282 mg/l) was found for *iso*-pentane in Charles-River rats (groups of 5 male and 5 female animals) after exposure for 4 hours to nominal concentrations of 842, 1241, 1423 and 1842 mg/l (corresponding to 277 860, 409 530, 469 590 and 607 860 ml/m^3). The recovery period was 14 days. Anaesthesia occurred 10 minutes after the start of exposure and persisted until the end of the exposure period or the animal's death. The survivors recovered within 20 minutes. Tremor was observed before death in the animals that died. At autopsy, the lungs of the rats exposed to *iso*-pentane concentrations of 1423 mg/l did not collapse after the thorax was opened; this was considered to be related to the exposure to *iso*-pentane (no other details). There were no other findings (Galvin and Marashi 1999 b).

In mice, *iso*-pentane was slightly narcotic at 90 000 and 110 000 ml/m^3 (269 100 and 328 900 mg/m^3) after 11.6 and 3.0 minutes; no lethal effects occurred after exposure for two hours. These effects occurred at concentrations of 130 000 ml/m^3

(388 700 mg/m^3) and above (2 of 10 animals); 50% of the 10 animals used died after 140 000 ml/m^3 (418 600 mg/m^3) (Stoughton and Lamson 1936). A study of the irritative effects on the respiratory tract of *iso*-pentane is described by Galvin and Marashi (1999 b). Four male CD-1 mice were exposed head-only to *iso*-pentane concentrations of 32 540 mg/m^3 and the effects of the exposure on the respiratory tract in each mouse were recorded using a plethysmograph. After exposure for one minute and an interval of 10 minutes, the animals were exposed for a further minute followed by an interval of 5 minutes. No irritative effects were observed. Stoughton and Lamson (1936) observed slight narcosis after 11.6 minutes in 6 mice exposed to *iso*-pentane concentrations of 90 000 ml/m^3 (269 100 mg/m^3). Two of 10 animals died after exposure for 2 hours to *iso*-pentane concentrations of 13 000 ml/m^3 (388 700 mg/m^3).

In mice exposed for 2 hours, *tert*-pentane concentrations of 200 000 ml/m^3 (598 000 mg/m^3) produced slightly narcotic effects after 30 minutes, and after exposure to 270 000 ml/m^3 (807 300 mg/m^3) narcosis after 3 minutes. After exposure to 340 000 ml/m^3 (1 016 600 mg/m^3) for 2 hours 40% (2 of 5 animals) died (Stoughton and Lamson 1936).

5.1.2 Ingestion

The toxicity of *n*-pentane (purity > 95%) was investigated in the rat according to Annex V, Part B.1 of the EU guideline (European Commission 1993) after oral administration of doses of up to 2000 mg/kg body weight. One rat died one hour after administration as a result of an error during intubation. The clinical symptoms observed were oral and nasal discharge, swollen abdomen, anogenital staining and soft or mucus stools. The remaining nine animals survived the end of the study (14 days); the gross pathological examination after killing the animals yielded no findings. The LD_{50} is stated by the authors to be greater than 2000 mg/kg body weight (McKee et al. 1998).

5.1.3 Dermal absorption

The dermal penetration rate of *n*-pentane through excised rat skin is 0.519 nmol/min and cm^2 (73.4 ng/min and cm^2) with a lag time of 3.11 hours (Tsuruta 1982).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

In an exposure chamber, groups of 10 male Crl:CD®BR rats were exposed to *n*-pentane concentrations of 0, 1000, 3000 or 10 000 ml/m^3 (purity 99.5%–99.6%) for

6 hours a day on 5 days a week for two weeks. Analytical determination of the exposure concentrations yielded *n*-pentane concentrations of 990 ± 11, 3100 ± 160 and 9900 ± 170 ml/m^3 (2960 ± 33, 9270 ± 478 and 29 600 ± 508 mg/m^3). Five animals per group were killed after the tenth exposure, the remaining animals after a 14-day observation period. Toxicity, behaviour, body weights, clinical pathology, gross and microscopic pathology and organ weights were investigated. No conspicuous clinical findings were observed and there were no relevant changes in body weights. The treated animals behaved normally in the functional observational battery (FOB). Increases (about 10%) in the concentrations of calcium and phosphorus in serum were found in the animals exposed to *n*-pentane concentrations of 3000 and 10 000 ml/m^3, which were reversible within the two-week observation period. Pathological changes were not observed. A NOAEL (no observed adverse effect level) of 1000 ml/m (2990 mg/m^3) is given by the authors for *n*-pentane, taking the reversible changes in both clinical parameters into account (Stadler et al. 2001).

On the basis of the results of a range-finding study (concentrations in the lower explosive limit range), *n*-pentane concentrations of 0, 5000, 10 000 or 20 000 mg/m^3 (purity > 95%) (analysed values 5097 ± 79, 10 203 ± 151 and 20 483 ± 734 mg/m^3) were used in the 90-day inhalation study performed according to Annex VIII of the EU guideline (European Commission 1993). Groups of 10 male and 10 female Sprague Dawley rats were exposed in whole-body chambers for 6 hours a day on 5 days a week for 13 weeks. Haematological and clinico-chemical parameters were determined immediately before killing the animals. The adrenal glands, brain, epididymis, kidneys, liver, lungs, trachea, prostate gland, seminal vesicles with coagulation glands, spleen, testes, ovaries, thymus and uterus were weighed. The tissue samples listed in the guideline were taken for microscopic examination from the animals of the highest exposure group and the controls. All animals survived. The observed clinical symptoms , a statistically significant increase in food consumption and body weight gains, were considered by the authors to be incidental. For the parameters organ weights, haematology and clinical chemistry, there was no evidence that the treatment had had any influence. Ophthalmological and microscopic examination of the organs and tissues yielded no findings. The NOAEL for *n*-pentane given by the authors is 20 000 mg/m^3 (6600 ml/m^3) (McKee et al. 1998).

No effects on the kidneys of rats were found by the end of a study after 90 days inhalation exposure to a mixture of *iso*-pentane and *iso*-butane (50:50 percent by weight) in concentrations of up to 4500 ml/m^3. However, male rats that were killed after 28 days did show slight signs of nephropathy (Aranyi et al. 1986). This study cannot be used in the evaluation as the animals were exposed to a mixture of substances.

To study the neurotoxicity of *n*-pentane, male Wistar rats (number not stated) were exposed to *n*-pentane (purity over 99%), *n*-hexane or *n*-heptane in an exposure chamber for 12 hours a day on 7 days a week for 16 weeks. Determination of the concentrations by gas chromatography yielded concentrations of 3080 ± 200 ml/m^3 (corresponding to 9210 ± 600 mg/m^3) for *n*-pentane. The conduction velocity of the tail nerves was used as a parameter for the functional state

of the peripheral nerves. The tail nerve was stimulated by pulses of 0.3 milliseconds in duration. Two animals from the *n*-hexane group and one animal from each of the other groups were subjected to morphological examination after the end of exposure. During exposure, the animals exposed to *n*-pentane behaved normally. Unlike in the animals exposed to *n*-hexane, no signs of neurotoxicity, determined via the nerve conduction velocity, were observed in the group exposed to *n*-pentane. The muscles of the lower leg and the tail and tibial nerves were examined using light and electron microscopy. No changes were found (Takeuchi et al. 1981).

Six to nine male Sprague Dawley rats were exposed for 9 hours a day on 5 days a week for 30 weeks to *n*-pentane concentrations of 3000 ml/m^3 (8970 mg/m^3) (purity 99%). At specified times, the animals were weighed and subjected to a physiological test for neuromuscular function in which the degree to which the hind limbs splayed on landing after the animal was dropped from a height of 32 cm was determined. To determine the metabolites in urine, 2 to 3 animals were kept in metabolic cages. A number of animals were killed at specific times for histological examination of the nerve tissue. No signs of neuropathy were observed in any of the animals. There was a difference in the body weight gains of the exposed animals and the controls. In the test for neuromuscular functions, great individual differences in the animals were found. Histological investigation of the nerve tissue yielded no findings. The results of the urinalysis regarding metabolites were not given (Frontali et al. 1981).

5.2.2 Ingestion

After groups of 10 male Fischer rats were given gavage doses of *n*-pentane of 0, 500 and 2000 mg/kg body weight for 4 weeks, 40% of the rats in the high dose group and 20% of those in the low dose group were dead. The absolute kidney weights were significantly lower in the treated animals. Gross pathological examination revealed varying lesions in the stomach region, liver and kidneys. Histopathological examination of the kidneys for hyaline droplet formation (by staining a tissue section with Mallory-Heidenhain solution) and epithelial regeneration and tubular dilation (by staining a second tissue section with eosin and haematoxylin) yielded no unusual findings. *iso*-Pentane was also investigated in this study at the same dose levels. *iso*-Pentane was likewise not found to be nephrotoxic in doses of 500 mg/kg body weight. Ninety percent of the animals died after doses of 2000 mg/kg body weight. The results of the kidney examination ("nephropathy score") are not given for this dose. (API 1985; Halder et al. 1985). The API (1985) study bears a note that it was taken out of the API publication series. The authors state that the results could be out of date. No serious deficiencies could be found after a review of the study, however.

5.3 Local effects on skin and mucous membranes

The effects of *n*-pentane (purity > 95%) on rabbit skin was tested according to the Draize recommendations, the guidelines of the European Commission (1993) and those of the OECD (1987). Forty-five minutes after application of the substance, erythema with a score of 1 was found in most of the animals, and with a score of 2 in one animal. After 24 hours, erythema with an average score of 0.83 was still visible in 4 animals and erythema with a score of 1 in one animal. After 48 hours, erythema with a score of 2 was observed in one animal (average score 0.33). Erythema was still found after 72 hours, but no longer after 7 days. The overall primary irritation score according to Draize (maximum score: 4) was 0.67 (McKee et al. 1998).

In another test, the effects of *n*-pentane (purity > 95%) on the eye were investigated. The test was carried out according to Annex V, Section B.5 of the EU guideline (European Commission 1993). One hour after application of the substance, reddening of the conjunctiva was found in all three animals, in addition to chemosis (circular conjunctival swelling) and pus in one animal. Redness was the only finding after 24 hours; the scores (determined according to Draize) for eye irritation were between 2 and 4, the average score was 1.33. After 48 hours, redness was found in only one animal, the average score for eye irritation was 0.33 (maximum score: 110). There were no findings after 72 hours (McKee et al. 1998).

5.4 Allergenic effects

A Magnusson-Kligman test was carried out with 20 white Hartley guinea pigs according to Annex V, Section B.6 of the EU guideline (European Commission 1993). A surface area of 4 × 6 cm of skin was shaved in the scapular region of the animals. Each animal was given an intradermal injection of 50/50 (v/v) Freund's complete adjuvant/water, *n*-pentane (5%) in ethanol and a mixture of 5% *n*-pentane in 50/50 (v/v) Freund's complete adjuvant/water. The 20 animals of the vehicle control were also given these injections, but without *n*-pentane. The positive control comprised 15 animals, to which a 2% solution of dinitrochlorobenzene (DNCB) in a 70/30 mixture of ethanol and acetone was administered. One week after the injections, the skin of the animals was shaved again and after the application of 0.5 ml *n*-pentane was covered with an occlusive dressing for 48 hours. Two weeks later, 0.4 ml of a 1% or 100% *n*-pentane solution was applied to untreated areas of skin. The animals were bandaged again and the dressing removed after 24 hours for immediate assessment, and after a further 24 hours for subsequent assessment of the skin. No apparent differences between the animals of the vehicle control and the treated animals were found. Sensitization was observed in the animals of the positive control. In this test, *n*-pentane was not found to have sensitizing potential (McKee et al. 1998).

5.5 Reproductive toxicity

In a dose-finding assay for a study of the developmental toxicity of *n*-pentane, gavage doses (purity > 95%) in corn oil of 250, 500, 750 or 1000 mg/kg body weight per day (duration not specified) were administered to 7 pregnant animals. In the authors' opinion there were no noteworthy findings in the foetuses; in the available publication, however, no corresponding data, for either the dams or the foetuses, are to be found which could support this (McKee et al. 1998).

The subsequent main study of the developmental toxicity of *n*-pentane (McKee et al. 1998) was carried out according to the 1987 EU test guideline (European Commission 1987). Gavage doses of *n*-pentane (purity > 95%) in corn oil of 100, 500 and 1000 mg/kg body weight were administered to groups of 25 pregnant Sprague Dawley rats once a day on gestation days 6 to 15. The rats in the control group were given corn oil only. The animals were killed on day 21 of gestation, and the foetuses removed by caesarean section. After dissection, all dams were subjected to gross pathological examination, their uterus weight was determined, the uterus content examined and the implant status determined. After determining their sex, all live foetuses were weighed and examined for external malformations. After this, around half of the foetuses of each litter were assessed for organ changes. In addition, the head of these foetuses after corresponding preparation was investigated for anomalies. The remaining foetuses were eviscerated and processed for skeletal staining. The skeletons were investigated for the presence of malformations and ossification variations.

No substance-related mortalities occurred, and there were no unusual clinical or autopsy findings in the dams. One control animal and one animal in the group given 100 mg/kg body weight gave birth before the determined time and were therefore killed prematurely; the litter data of these two animals were not included in the further analysis of the data. There were no statistically significant differences in the food consumption, body weights, body weight gains (absolute and corrected), uterus weights and pregnancy parameters of the dams of the control and the treated groups. Nor were any statistically significant differences found in the foetuses or litters of the various groups with regard to body weights, the occurrence of external, skeletal or total malformations or malformation of the organs, or the degree of ossification of the skeletons (McKee et al. 1998).

Groups of 7 or 8 female Crl:CD®BR rats were exposed (whole body) to *n*-pentane concentrations of 0, 1000, 3000 or 10 000 ml/m^3 (purity 99.5% to 99.6%) for 6 hours a day on days 6 to 15 of gestation. The analysed values were 990 ± 11, 3100 ± 160 and 9900 ± 170 ml/m^3 (2960 ± 33, 9270 ± 478 and 29 600 ± 508 mg/m^3). The dams were sacrificed using carbon dioxide and subjected to gross pathological examination. After the opening of the uterus, the number and position of live, dead and resorbed implants was determined, as well as the number of *corpora lutea* per ovary. In the animals not pregnant, the uterus was stained with ammonium sulfide to identify very early resorptions. After determining the sex and weight of the foetuses, they were examined for external malformations.

All female rats survived the exposure period. No differences were found in the treated and untreated animals as regards body weight gains and food consumption, and clinical symptoms. The incidence of resorptions was slightly increased in the two high exposure groups compared with that in the controls. However, as this was not concentration-dependent, and the values were within the upper range of historical control data, it was regarded as a spontaneous finding. Likewise, no effects were recognizable in the remaining pregnancy parameters (including incidence of pregnancy, number of implants, *corpora lutea* and live foetuses/dam). The foetus weights were slightly reduced in the treated groups compared with those of the control group. However, the authors do not attribute any toxicological relevance to these findings, as they were not concentration-dependent and without statistical significance. Furthermore, no external malformations were recognizable in the offspring (Hurtt and Kennedy 1999). From the results of this study with its limited number of animals and restricted study scope, the authors therefore reach the conclusion that, under the selected exposure conditions, *n*-pentane has no adverse effects on dams, pregnancy parameters or foetuses.

5.6 Genotoxicity

To determine the mutagenicity of *n*-pentane and *iso*-pentane a modified test with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 was carried out in the absence and presence of a metabolic activation system. The agar-agar dishes containing the strains were exposed to the test substance in the gaseous phase in a dessicator for 6 hours. *n*-Pentane was found to be cytotoxic in concentrations of 25% and 50%, so that additional investigations were carried out with 1%, 2%, 5%, 8% and 10% *n*-pentane in air. Mutagenic effects were not observed. *iso*-Pentane was toxic in concentrations of 10% and above; additional investigations with 1%, 2%, 5% and 8% *iso*-pentane in air yielded no evidence of a mutagenic potential (Kirwin et al. 1980).

A test for chromosomal aberrations in CHO cells was carried out with *n*-pentane according to Annex V, Section B.10 of the EU guideline (European Commission 1993). As *n*-pentane has a boiling point of 37°C, flasks sealed with septa were used for incubation. Based on the results of a pilot study, concentrations of 300 to 1500 µl/ml were used. The test concentrations were not verified analytically. The test was carried out both in the absence and presence of a metabolic activation system (rat liver S9). Dimethylbenz[*a*]anthracene (DMBA) and methylnitronitrosoguanidine (MNNG) were used as positive controls. In each case, 200 metaphases were investigated. The cultures treated with 300, 1000, 1200 and 1500 µg/ml, which were used without metabolic activation, were harvested after 20 and 44 hours and evaluated. To evaluate the preparation with metabolic activation, the cultures treated with 600, 900 and 1100 µg/ml were selected.. There were no significant differences in the 20-hour repeat without metabolic activation or in any of the 44-hour

assessments. In the 20-hour cultures with metabolic activation, an increasing, dose-dependent trend in the percentage of changed (abnormal) cells was found, which was significant in the cells treated with 1200 µg/ml and 1500 µg/ml compared with the number found in the control cultures (McKee et al. 1998).

On account of these somewhat questionable results, as the authors describe, also a micronucleus test was carried out in conjunction with the 90-day inhalation study performed with *n*-pentane (McKee et al. 1998). The animals were killed one day after the final exposure, and one femur from 5 male and 5 female rats per group was removed and prepared. Another group of 5 rats, which had been given oral cyclophosphamide doses of 20 mg/kg body weight 3 times for 3 days, served as positive controls. The percentage of polychromatic erythrocytes in the entire population of erythrocytes was determined by counting 1000 polychromatic erythrocytes and the normochromatic erythrocytes. 2000 polychromatic erythrocytes per animal were investigated for the presence of erythrocytes with micronuclei. For the animals exposed to *n*-pentane, the test yielded negative results; the positive controls produced positive results (McKee et al. 1998).

5.7 Carcinogenicity

There are no data for the carcinogenicity of any pentane isomer in animals.

6 Manifesto (MAK value, classification)

Like other hydrocarbon solvents, pentane induces central nervous depression at high levels of exposure. There are no precise data available for the threshold level in humans . In a 13-week study with rats, no effects could be found for *n*-pentane at the highest concentration tested of 6660 ml/m^3 (20 000 mg/m^3). The MAK value for *n*-hexane was set at 50 ml/m^3 on account of its specific neurotoxicity, that for the hexane isomers at 200 ml/m^3 and for *n*-heptane at 500 ml/m^3. The MAK value for *n*-butane is 1000 ml/m^3, and that for propane 1000 ml/m^3.

As no effects were found in a 13-week study with rats exposed to concentrations of up to more than 6000 ml/m^3, and the toxicity of the branched compounds has been observed to be lower than that of *n*-pentane, the MAK value of 1000 ml/m^3 has been provisionally retained for all pentane isomers. As no irritative effects are to be expected in the concentration range of the MAK value, pentane has been classified in Peak Limitation Category II with an excursion factor of 2.

Two prenatal developmental toxicity studies with rats exposed on gestation days 6 to 15 are available. In one study, no maternal or developmental toxicity was found after oral doses of *n*-pentane of up to 1000 mg/kg body weight. In the other study, the animals were exposed via inhalation to *n*-pentane concentrations of 1000, 3000 or 10 000 ml/m^3. In the two high exposure groups only slight changes occurred,

which were not concentration-dependent and regarded by the authors not to be adverse. Therefore, developmental toxicity is not to be expected if the MAK value of 1000 ml/m^3 is observed. However, as studies involving a second species are not available, the substance is classified in Pregnancy Risk Group D, tending towards C.

The studies did not yield any evidence of genotoxic effects. There are no data available regarding carcinogenic effects. There are no data available for sensitization in humans, but a maximization test in guinea pigs yielded negative results. Therefore, the substances are not designated with "Sh", and as no data is available for sensitization of the respiratory tract nor with "Sa".

Assuming a respiratory volume of 10 m^3 per shift and the absorption of 50% of the substance, inhalation exposure to pentane for 8 hours at the level of the MAK value of 1000 ml/m^3 (3000 mg/m^3) would result in the absorption of 15 000 mg. Compared with this, the level of dermal penetration calculated according to the more favourable model is so low that observance of the MAK value provides sufficient protection even when there is additional skin contact with solutions containing pentane. Extended periods of dermal exposure to undiluted pentane can be excluded because of its high vapour pressure. Pentane is therefore not designated with an "H".

No data are available which justify classification of the substance in one of the categories for germ cell mutagens.

References

ACGIH (American Conference of Governmental Industrial Hygienists) (2001) Pentane, all isomers. Documentation of TLVs and BEIs, ACGIH, Cincinnati, OH, USA

API (American Petroleum Institute) (1985) Four-week oral nephrotoxicity screening study in male F344 rats. Borriston Laboratories Inc Temple Hills, Maryland, Contract PS-53, American Petroleum Institute, Washington DC

API (American Petroleum Institute) (1987) Studies on the absorption of inhaled hydrocarbon vapors. Inhalation Toxicology Research Institute Lovelace Biomedical and Environmental Research Institute, Albuquerque, New Mexico, Contract PS-56, American Petroleum Institute, Washington DC

Aranyi C, O'Shea WJ, Halder CA, Holdsworth CE, Cockrell BY (1986) Absence of hydrocarbon-induced nephropathy in rats exposed subchronically to volatile hydrocarbon mixtures pertinent to gasoline. *Toxicol Ind Health* 2: 85–98

Daugherty MS, Ludden TM, Burk RF (1988) Metabolism of ethane and pentane to carbon dioxide by the rat. *Drug Metab Dispos* 16: 666–671

European Commission (1987) Commission Directive of 18 November 1987 adapting to technical progress for the ninth time Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packing and labelling of dangerous substances, 87/302/EEC, http://eudor.eur-op.eu.int

European Commission (1993) Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packing and labelling

of dangerous substances, Annex VIII, http://eudor.eur-op.eu.int

Filser JG, Bolt HM, Muliawan H, Kappus H (1983) Quantitative evaluation of ethane and n-pentane as indicators of lipid peroxidation *in vivo*. *Arch Toxicol* 52: 135–147

Filser JG, Csanády GA, Pott F (1996) Inhalation kinetics and endogenous production of *n*-pentane in rat and man. *Toxicol Lett* 88: 44

Fiserova-Bergerova V, Pierce JT, Droz PO (1990) Dermal absorption potential of industrial chemicals: criteria skin notation. *Am J Ind Med* 17: 617–635

Frommer U, Ullrich V, Staudinger H (1970) Hydroxylation of aliphatic compounds by liver microsomes, I. *Hoppe-Seyler's Z Physiol Chem* 351: 903–912

Frontali N, Amantini MC, Spagnolo A, Guarcini AM, Saltari MC, Brugnone F, Perbellini L (1981) Experimental neurotoxicity and urinary metabolites of the C5-C7 aliphatic hydrocarbons used as glue solvents in shoe manufacture. *Clin Toxicol* 18: 1357–1367

Fühner H (1921) Die narkotische Wirkung des Benzins und seiner Bestandteile (Pentan, Hexan, Heptan, Octan) (The narcotic effects of petrol and its components (pentane, hexane, heptane, octane)) (German). *Biochem Z* 115: 235–261

Galvin JB, Marashi F (1999 a) *n*-Pentane. *J Toxicol Environ Health A* 58: 35–56

Galvin JB, Marashi F (1999 b) 2-Methylbutane (Isopentane). *J Toxicol Environ Health A* 58: 23–33

Galvin JB, Panson R (1999) Neopentane (2,2-dimethylpropane). *J Toxicol Environ Health A* 58: 75–80

Gaultier M, Rancurel G, Piva C, Efthymiou ML (1973) Polyneuritis and aliphatic hydrocarbons (French). *J Eur Toxicol* 6: 294–296

Glowa JR (1991) Behavioral toxicology of volatile organic solvents V. Comparison of the behavioral and neuroendocrine effects among n-alkanes. *J Am Coll Toxicol* 10: 639–646

Guy RH, Potts RO (1993) Penetration of industrial chemicals across the skin: a predictive model. *Am J Ind Med* 23: 711–719

Halder CA, Holdsworth CE, Cockrell BY, Piccirillo VJ (1985) Hydrocarbon nephropathy in male rats: identification of the nephrotoxic components of unleaded gasoline. *Toxicol Ind Health* 1: 67–87

Hau KM, Connell DW, Richardson BJ (1999) Mechanism of acute inhalation toxicity of alkanes and aliphatic alcohols. *Environ Toxicol Pharmacol* 7: 159–167

HSDB (Hazardous Substances Data Bank) (2004) Data bank excerpt, http://www.cas.org/ONLINE/DBSS/hsdbss.html

Hurtt ME, Kennedy Jr GL (1999) A limited developmental toxicity study of pentane by inhalation in the rat. *Food Chem Toxicol* 37: 565–567

Kirwin CJ, Thomas WC, Simmon VF (1980) *In vitro* microbiological mutagenicity studies of hydrocarbon propellants. *J Soc Cosmet Chem* 31: 367–370

McKee R, Frank E, Heath J, Owen D, Przygoda R, Trimmer G, Whitman F (1998) Toxicology of *n*-pentane (CAS No. 109-66-0). *J Appl Toxicol* 18: 431–442

OECD (Organisation for Economic Co-Operation and Development) (1987) Guidelines for Testing of Chemicals (1987 and subsequent revisions), OECD, Paris, France

OECD (Organisation for Economic Co-Operation and Development) (2001) *n*-Pentane. Screening Information Dataset Dossier, Draft, OECD, Paris

Oettel H (1936) Einwirkung organischer Flüssigkeiten auf die Haut (The action of organic liquids on the skin) (German). *Arch Exp Pathol Pharmakol* 163: 641–696

Perbellini L, Brugnone F, Caretta D, Maranelli G (1985) Partition coefficients of some industrial aliphatic hydrocarbons (C5-C7) in blood and human tissues. *Br J Ind Med* 42: 162–167

Stadler JC, O'Neill AJ, Elliott GS, Kennedy Jr GL (2001) Repeated exposure inhalation study of pentane in rats. *Drug Chem Toxicol* 24: 75–86

Stoughton RW, Lamson PD (1936) The relative anaesthetic activity of the butanes and pentanes. *J Pharmacol Exp Ther* 58: 74–77

Swann Jr HE, Kwon BK, Hogan GK, Snellings WM (1974) Acute inhalation toxicology of volatile hydrocarbons. *Am Ind Hyg Assoc J* 35: 511–518

Takeuchi Y, Mabuchi C, Takagi S (1975) Polyneuropathy caused by petroleum benzine. *Int Arch Arbeitsmed* 34: 185–197

Takeuchi Y, Ono Y, Hisanaga N, Kitoh J, Sugiura Y (1981) A comparative study of the toxicity of n-pentane, *n*-hexane, and n-heptane to the peripheral nerve of the rat. *Clin Toxicol* 18: 1395–1402

Tsuruta H (1982) Percutaneous absorption of organic solvents. III. On the penetration rates of hydrophobic solvents through the excised rat skin. *Ind Health* 20: 335–345

Van Rij AM, Wade CR (1987) The metabolism of low molecular weight hydrocarbon gases in man. *Free Radical Res Commun* 4: 99–103

completed 03.02.2004