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Trimethylpentane (all isomers)

MAK Value Documentation, addendum – Translation of the German version from 2017

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated trimethylpentane (all isomers), considering all toxicity endpoints. Available unpublished study reports and publications are described in detail.

The re-examination determined that it is difficult to draw final conclusions from a carcinogenicity study of a mixture of 542 hydrocarbons and from mechanistical studies with some of their single components. Thus, the assignment to Carcinogen Category 3 A has been withdrawn. The critical effect is the acute effect on the central nervous system in rats. The NOAEC after 60 min inhalation is 500 ml 2,2,4-trimethylpentane/m³. Experimental data from structurally analogous n-alkanes and iso-alkanes lead to the assumption that the concentration of 2,2,4-trimethylpentane in the brain after 8 hours will be about twice as high as after one hour. The short half-life in the brain, estimated to be about one hour, does not predict an accumulation during the work week. The same assumptions are made for the other trimethylpentane isomers. Thus, taking into consideration uncertainties in the extrapolation of animal to human data, a MAK value of 100 ml/m³ (470 mg/m³) is set for all trimethylpentane isomers. As the critical effect is systemic, trimethylpentane isomers are assigned to Peak Limitation Category II. The excursion factor of 2 is set as the estimated half-life in the brain is one hour or even less. Prenatal developmental toxicity studies with trimethylpentane isomers are not available. For structurally analogous C8-isoalkanes the NOAEC for developmental toxicity in rats is more than 1200 ml/m³. Acute neurotoxicity is critical, but the consequences of acute neurotoxic effects on in-utero development of the nervous system are not knownand studies on developmental neurotoxicity of C8-alkanes are not available. Thus, trimethylpentane isomers are classified in Pregnancy Risk Group D. There are no clinical data and no data in animals concerning the sensitizing potential of trimethylpentane isomers. In analogy to n-heptane, skin contact is not expected to contribute significantly to systemic toxicity.

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Keywords

trimethylpentane (all isomers); 2,2,3-trimethylpentane; 2,2,4-trimethylpentane; 2,3,3-trimethylpentane; 2,3,4-trimethylpentane; toxicokinetics; metabolism; developmental toxicity; peak limitation; prenatal toxicity; absorption through the skin; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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Trimethylpentane (all isomers)

2,2,3-Trimethylpentane [564-02-3]
2,2,4-Trimethylpentane [540-84-1]
2,3,3-Trimethylpentane [560-21-4]
2,3,4-Trimethylpentane [565-75-3]

Supplement 2017

MAK value (2016)	**100 ml/m³ (ppm) ≙ 470 mg/m³**
Peak limitation (2016)	**Category II, excursion factor 2**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2016)	**Pregnancy Risk Group D**
Germ cell mutagenicity	**–**
BAT value	**–**
log K_{OW}[1]	for 2,2,4-trimethylpentane 4.08 (calculated; ECHA 2015)
Solubility in water at 25 °C	for 2,2,4-trimethylpentane 2.2 mg/l (ECHA 2015)

For 2,2,4-trimethylpentane there is documentation available from 1989 (documentation "2,2,4-Trimethylpentane" 1990). The other three isomers are included in the supplement from 2004 on carcinogenicity (supplement "Trimethylpentane (all isomers)" 2004).

Trimethylpentane isomers are constituents of unleaded petrol. They make up about 11.75% of the formulation used in the carcinogenicity study (MacFarland et al. 1984).

In 2004 the carcinogenicity of trimethylpentane isomers was re-evaluated on the basis of new studies. In the supplement from 2004 (supplement "Trimethylpentane (all isomers)" 2004), the critical effect was considered to be the carcinogenic effect on the liver of female B6C3F1 mice induced by unleaded petrol (Magaw et al. 1993; MacFarland et al. 1984). The development of liver tumours is attributed to a non-genotoxic mechanism because unleaded petrol and 2,2,4-trimethylpentane are not genotoxic and their structures do not suggest this. To investigate which constit-

1) Octanol/water partition coefficient.

uents of unleaded petrol are responsible for the liver tumour-promoting effect in female mice, female B6C3F1 mice were given intragastric doses of unleaded petrol and four fractions separated according to the boiling range, and subsequently the bromodeoxyuridine-labelling index in the liver was determined. Both unleaded petrol and the fraction (boiling range fraction 3: 100–132 °C) containing 2,2,3-trimethylpentane, 2,3,4-trimethylpentane and 2,2,4-trimethylpentane (boiling points: 2,2,3-trimethylpentane: 110 °C; 2,2,4-trimethylpentane: 99.2 °C; 2,3,4-trimethylpentane: 113.5 °C; SRC 2013 a, b, c) increase the bromodeoxyuridine-labelling index (no data for 2,3,3-trimethylpentane). The other three fractions (boiling ranges: fraction 1: < 66 °C, fraction 2: 66–100 °C, fraction 4: > 132 °C) do not change the bromodeoxyuridine-labelling index. In addition, the individual substances 2,2,3-trimethylpentane, 2,3,4-trimethylpentane and 2,2,4-trimethylpentane were tested in this system. These trimethylpentane isomers increase the bromodeoxyuridine-labelling index by about 150% to 400%. The increase (by about 20%) in the relative liver weights of the treated animals compared with those of the control animals was statistically significant. Body weights and serum enzymes were not affected by treatment with the trimethylpentane isomers. The authors concluded that the three trimethylpentane isomers are mitogenic constituents of unleaded petrol and co-responsible for its mitogenic effect (Standeven and Goldsworthy 1994). This suggests that the trimethylpentane isomers can induce liver tumours resulting from the increase in cell proliferation. As there is no NOAEL (no observed adverse effect level) available for the increase in proliferation, no MAK value was derived, and the isomers were classified in Carcinogen category 3A in 2004 (supplement "Trimethylpentane (all isomers)" 2004).

A re-evaluation of the carcinogenic effects of the substance carried out in 2006 confirmed its classification in Carcinogen category 3A (supplement "Trimethylpentane (all isomers)" 2006).

A re-examination of the composition of the petrol formulations used in the carcinogenicity study in mice and the mechanistic studies makes a re-evaluation necessary.

Toxicokinetics and Metabolism

Absorption, distribution, elimination

2,2,4-Trimethylpentane is rapidly and completely absorbed from the gastrointestinal tract (supplement "Trimethylpentane (all isomers)" 2004).

In male and female F344 rats, about 30% of the dose was recovered in the urine 48 hours after gavage administration of single doses of 5-^{14}C-labelled 2,2,4-trimethylpentane of 500 mg/body weight (Charbonneau et al. 1987). In animals of the same species given the same dose, 67% of the dose was detected in the urine of male animals and 50% in that of female animals after 72 hours (Kloss et al. 1985). In these two studies there was an accumulation of radioactivity in the kidneys (Charbonneau et al. 1987; Kloss et al. 1985). The concentration in the brain was not measured in either of the studies. 2,2,4-Trimethylpentane was not found to accumulate in the adipose tissue in the two gavage studies.

Using the models of Fiserova-Bergerova et al. (1990), Guy and Potts (1993) and Wilschut et al. (1995) fluxes of 43, 0.63 and 0.22 µg/cm² and hour, respectively, were predicted for a saturated aqueous solution of 2,2,4-trimethylpentane. Assuming the exposure of 2000 cm² of skin for one hour, the amounts absorbed would be 86, 1.2 and 0.44 mg, respectively.

There are no studies of dermal absorption available for any of the four trimethylpentane isomers, or for any other octane isomers, but there is an in vitro study for the structurally similar *n*-heptane. Human skin was heat-treated and the epidermis was placed in a static diffusion cell. The receptor fluid used was physiological saline solution with 6% polyethylene glycol oleyl ether. To determine the penetration rate at the steady state, a dose of undiluted *n*-heptane of 1200 µl/cm² was used. To determine short-term fluxes after 10 and 60 minutes, 20 µl/cm² was used. The penetration rate at the steady state was 63.2 µg/cm² and hour. The penetration rate after 10 minutes was 113.3 µg/cm² and hour, after 60 minutes 22.1 µg/cm² and hour (Fasano and McDougal 2008). From this latter value, the absorption of 44 mg per 2000 cm² of skin and hour can be calculated. This value is not inconsistent with the values calculated for 2,2,4-trimethylpentane and is therefore assumed also for trimethylpentane.

Metabolism

The assumed metabolism of 2,2,4-trimethylpentane is shown in Figure 1 of the documentation from 1989 (documentation "2,2,4-Trimethylpentane" 1990).

Only 2,2,4-trimethylpentane and 2,3,4-trimethylpentane were investigated in rats. Mainly, an oxidative attack takes place at the C2 atom, the secondary alcohol is eliminated as a conjugate. The terminal methyl groups can also be oxidized and are detected as alcohols, aldehydes and carbonic acids (documentation "2,2,4-Trimethylpentane" 1990). In male and female F344 rats, the following main metabolites were found in urine after gavage administration: 2,4,4-trimethyl-2-pentanol, 2,4,4-trimethyl-1-pentanol, 2,4,4-trimethylpentanoic acid, 2,2,4-trimethyl-1-pentanol and 2,2,4-trimethylpentanoic acid (Charbonneau et al. 1987; documentation "2,2,4-Trimethylpentane" 1990). After gavage administration of 2,3,4-trimethylpentane to male F344 rats the following metabolites were identified in the urine: 2,3,4-trimethyl-1-pentanol, 2,3,4-trimethyl-1-pentanoic acid and 2,3,4-trimethyl-5-hydroxy-1-pentanoic acid (Olson et al. 1987; documentation "2,2,4-Trimethylpentane" 1990).

There are no data available for the other isomers.

Animal Experiments

Studies with single inhalation exposures to trimethylpentane isomers are listed in Table 1.

Studies with repeated inhalation exposure are not available.

Table 1 Short-term inhalation studies with trimethylpentane isomers

Species, strain, number per group	Exposure	Findings	References
rat, Long Evans, 7–10 ♂	0, 500, 1000 ml/m³, 2,2,4-TMP, vapour, head-only, single, 60 minutes	**500 ml/m³: NOAEC for acute neurotoxic effects**; **1000 ml/m³**: VEPs: markedly increasing reduction of the F2 (9 Hz) components during exposure, which continued for 1 hour after exposure; recovery unclear; PBPK: estimated TMP concentration in brain at 2500 ml/m³ < 0.2 mM after 62 minutes, not measured	Boyes et al. 2010
rat, Long Evans, 14 ♂	0, 500, 1000, 1500, 2000, 2500 ml/m³, 2,2,4-TMP, vapour, head-only, single, 62 minutes	**2000 ml/m³: NOAEC**; **2500 ml/m³**: recognition in the appetite-motivated visual signal detection task: accuracy of performance slightly ↓	Boyes et al. 2010
mouse, Swiss-Webster, ♂, number not specified	Limit Test, 2,2,4-TMP, vapour, whole-body, single, 30 minutes	**RD_{50} > 1000 ml/m³**	Stadler and Kennedy 1996
mouse, Swiss, 4, sex not specified	0, 1000, 2000, 4000, 8000, 16 000, 32 000, 64 000, 128 000 ml/m³, 2,2,4-TMP, vapour, whole-body, single, 5 minutes	**1000 ml/m³ and above**: severe irritation of the respiratory tract (no other details); **16 000 ml/m³**: sensory irritation and motor impairments, respiratory arrest: 1/4 during recovery, respiratory pattern similar to 4800 ml *n*-heptane/m³, no anaesthetic effect; **32 000 ml/m³**: respiratory arrest: 4/4 during exhalation phase within 4 minutes, which was interpreted as possible pulmonary irritation	Swann et al. 1974; documentation "2,2,4-Trimethylpentane" 1990

Table 1 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, mouse, guinea pigs, SD, CD-1, Hartley, 10 ♂, 10 ♀	0, 8322 ml/m³, 2,2,4-TMP, vapour, whole-body, single, 4 hours	**8322 ml/m³**: rat: no abnormalities up to 15 minutes, after 20 minutes convulsions, excessive lacrimation and salivation, laboured breathing, within 55 minutes all animals dead; mouse: after 20 minutes 1 animal dead, within 75 minutes all animals dead; guinea pigs: between 60 and 120 minutes 8/10 animals dead, necropsy: discoloration of the lungs in all animals, discoloration of the liver in 2/10	US EPA 2007

F2: "Frequency-double", the first harmonicfrequency at twice the stimulus rate; NOAEC: no observed adverse effect concentration; PBPK: physiologically-based pharmacokinetic model; TMP: trimethylpentane, VEPs: visually evoked potentials

Local irritation

The RD_{50} value in mice after exposure to **2,2,4-trimethylpentane** vapour for 30 minutes in whole-animal chambers was more than 1000 ml/m³ (Stadler and Kennedy 1996).

In mice exposed in whole-animal chambers for 5 minutes, severe irritation of the respiratory tract (no other details) was observed at the lowest 2,2,4-trimethylpentane concentration tested of 1000 ml/m³ and above. At concentrations of 16 000 ml/m³ and above apnoea occurred in one of four animals (Swann et al. 1974). As there are no more details available and determination of the RD_{50} value did not reveal respiratory depression at the concentration of 1000 ml/m³ (Stadler and Kennedy 1996), this data is not plausible and not included in the evaluation.

After exposure to a 2,2,4-trimethylpentane concentration of 8322 ml/m³ for 4 hours, rats and mice were found to be more sensitive than guinea pigs as regards local irritation (US EPA 2007). Only one concentration was tested.

In a study to determine eye irritation using test methods similar to OECD Test Guideline 405, 0.1 ml undiluted 2,2,4-trimethylpentane was administered to 6 New Zealand White rabbits. An irritation score of 0.67 on a scale of 0 to 4 was obtained for the conjunctiva in one animal and of 0 in each of the other animals and also for the cornea, iris and conjunctiva. The substance is therefore not regarded as irritating to the eye (ECHA 2015). Therefore, a strong potential for local irritation in the respiratory tract is not assumed. This is confirmed by the RD_{50} value determined (see above).

The C8 hydrocarbon ***n*-octane** can be used as a reference substance for comparing the local effects.

In CF1 mice, a 50% depression in the respiratory frequency was not observed up to *n*-octane concentrations of 11 700 ml/m³ after exposure for 10 minutes. From this, an RD_{50} value of 18 200 ml/m³ was derived (documentation "Octane and its isomers except trimethylpentane isomers" 2004).

In a 13-week inhalation study in 10 male and 10 female F344 rats per concentration group carried out according to OECD Test Guideline 413, the *n*-octane concentrations used were 0, 200, 560 or 1600 ml/m³. No effects were found up to the highest concentration tested. The NOAEC (no observed adverse effect concentration) for local effects is thus higher than 1600 ml *n*-octane/m³ (Sung et al. 2010).

Systemic effects

Effects on the central nervous system (CNS)

To investigate the acute neurotoxic effects, visually evoked potentials (VEPs) were recorded using electrodes implanted into male Long Evans rats viewing modulated visual patterns (0.16 cycles per degree visual angle, 60% contrast, 4.55 Hz appear/disappear). The rats were exposed to 2,2,4-trimethylpentane concentrations of 0, 500 and 1000 ml/m³ for 60 minutes. The effects on the VEPs were displayed with a high temporal resolution and recorded for up to 60 minutes after the exposure. During the 60-minute exposure to 1000 ml/m³, a marked reduction in the frequency-double (F2, the first harmonic frequency obtained at twice the stimulus rate,

9 Hz) occurred, which increased over time, and there was a general disturbance in the characteristic sinusoidal response profile (dispersion of wavelengths). During the 60-minute follow-up phase, this specific frequency band did not reach the level obtained under the control condition. At the concentrations of 500 and 1000 ml/m³, significant differences to the control condition were observed in some cases, also during the one-hour follow-up phase. A comparison of the trends was made difficult by the fact that there was marked variation, especially at 500 ml/m³. No examinations were carried out at later times, so that it is unclear whether further recovery took place (Boyes et al. 2010). The Commission has derived a NOAEC for acute neurotoxic effects of 500 ml 2,2,4-trimethylpentane/m³, which represents a conservative approach.

On the assumption that the effects of solvents on the CNS follow a common mechanism and that the concentration of the parent substance in the brain at the time of examination is relevant for the effects on VEPs, a physiologically based pharmacokinetic (PBPK) model was used to estimate the trimethylpentane concentration which has an effect similar to that of **toluene**. With exposure at a constant level, the corresponding trimethylpentane concentration was estimated to be between 3250 and 21 672 ml/m³. The study gives no information as to which toluene concentration the estimated concentration range should correspond and for which period of time it should apply (El-Masri et al. 2009). The low blood/air partition coefficient of trimethylpentane of 2.5 explains why trimethylpentane is less neurotoxic than toluene when the external concentrations are the same (Boyes et al. 2010).

Toluene also led to reduced VEP amplitudes in Long Evans rats (Boyes et al. 2007). A comparison of the two studies (Boyes et al. 2007, 2010) shows that the experiments with trimethylpentane focused more on the temporal effects, that is on the development of the effects at 1000 ml 2,2,4-trimethylpentane/m³ during the 60-minute exposure and the subsequent 60-minute follow-up phase without exposure. The study with toluene gave more attention to the concentration-dependency of the effects. Hardly any difference in the F2 amplitudes was found after 60 minutes for the four toluene concentrations. The effect after 120 minutes at the concentration of 1000 ml/m³ was similar to that at 4000 ml/m³ after 60 minutes. The estimated concentrations in the brain were 0.4 mM and 1.6 mM toluene (Boyes et al. 2007). The difference in the brain levels can be interpreted as a relative inaccuracy in the model of the dose–response relationship between the internal toluene concentration and the neurotoxic effect. The determined effect sizes are all above the values estimated for trimethylpentane, which lends support to the statement that toluene has a stronger effect than trimethylpentane. The difference in the effect sizes of toluene and trimethylpentane with regard to the acute effects on the VEPs is due, according to the data of Boyes et al. (2007, 2010), mainly to the different toxicokinetics of trimethylpentane, which leads to a lower concentration in the target organ. This is clearly shown, for example, by the difference in the fat/blood partition coefficients of the two substances. The reduction in the VEPs was reversible in the study with toluene (Boyes et al. 2007).

The neurobiological mechanisms of action of 2,2,4-trimethylpentane and toluene are unclear. The studies found no evidence of identical mechanisms of action and yielded no information regarding the size of the effects. The exposure of rats to

toluene concentrations of 1000 ml/m³ for 6 hours led to the deregulation of 226 genes (after 6 hours) and 3352 genes (after 18 hours) (Hester et al. 2011), which is suggestive of changes in a large number of signalling pathways. Many of these changes are associated with neuroplasticity (a special characteristic of synapses, neurons or even whole brain areas to reorganize themselves for the purpose of optimizing ongoing processes). Similar studies for trimethylpentane are not available. Therefore, quantitative extrapolation on the basis of effect size estimates cannot be carried out. For this reason, it is not possible to assess the substance in analogy to toluene. Furthermore, toluene belongs to a different class of chemical substances.

The lowest effect concentration found in the signal detection test in male Long Evans rats was 2500 ml 2,2,4-trimethylpentane/m³ after inhalation exposure for one hour (Boyes et al. 2010).

VEPs were not determined for the reference substance ***n*-octane**.

In a behavioural test with optical signals, the response rates were reduced at *n*-octane concentrations of more than 2000 ml/m³ (Glowa 1984). In a neurotoxicity study in which groups of 8 male Wistar rats were exposed by inhalation to *n*-octane concentrations of 0, 1400, 4200 or 14 000 mg/m³, no effects were observed on neuromuscular, sensorimotor, convulsive and excitatory parameters or on motor activity after 3-day inhalation exposure (8 hours/day) up to the highest concentration tested of 14 000 mg/m³ (2917 ml/m³) (Lammers et al. 2011). Using the same test system, the same research group also investigated not specified C^{7}-^{10} isoalkanes with the CAS number 90622-56-3 (97% C8 isomers) at concentrations of 0, 1400, 4200 or 14 000 mg/m³. Up to the highest concentration, this test mixture likewise did not cause neurotoxic effects (McKee et al. 2011). The results of the "classic" neurotoxicity study of McKee et al. (2011) and of the VEP recordings of Boyes et al. (2010) are more or less consistent. The determined effects are an expression of the acute neurotoxicity of trimethylpentane and other C8 isoalkanes. However, in the "classic" neurotoxicity studies of McKee et al. (2011) and Lammers et al. (2011) the visual discrimination performance and the functional observation battery were recorded or carried out after the exposure. Meta-analyses of the acute effects of the four solvents toluene, trichloroethylene, tetrachloroethylene and 1,1,1-trichloroethane (Benignus et al. 2009) confirm that the response of VEPs to acute neurotoxicity is more sensitive than that of other target parameters (test battery).

Effects on the liver and kidneys

Typically, branched hydrocarbons cause liver effects, such as the induction of metabolizing liver enzymes and increased liver weights, and kidney effects, such as nephropathy.

Other **C8 isoalkanes** can be used as reference substances for the systemic effects of the branched C8 hydrocarbon trimethylpentane. In the following study, a mixture of branched hydrocarbons produced synthetically from light gases was used. This mixture contained only a very small proportion of aromatic hydrocarbons and is liquid at room temperature (Exxon Mobil Corporation 2013). The test substance used consisted of about 80% to 90% 2,2,4-trimethylpentane, the total content of trimethylpentane isomers was more than 95% (Adenuga 2016).

Groups of 35 male and 35 female Sprague Dawley rats were exposed in whole-animal chambers to C8 isoalkanes in vapour form in concentrations of 0, 400 or 1200 ml/m³ for 12 weeks (6 hours/day, 5 days/week). To generate the test chamber atmosphere, dry air was passed at different flow rates over the test substance contained in gas washing bottles to evaporate suitable amounts of the test substance. The vapour–air mixtures were subsequently directed to a port connected before the exposure chamber, where they were further diluted prior to being introduced into the exposure chamber. The analytically determined average concentrations were 385 and 1180 ml/m³. Samples from the exposure chambers were taken by adsorption of the test substance on activated carbon filters and subsequent desorption with tetrahydrofuran. The controls were subjected to sham exposure. After 4 and 8 weeks, 10 animals per concentration and sex were killed and examined (clinical chemistry, haematology, necropsy, histological examination of around 28 organs/tissues including the lungs in the controls and high concentration group; liver: 2 planes of section, nose and larynx not examined). The remaining animals were examined in the same way at the end of the study after 12 weeks. In the male animals, the absolute liver weights (385 ml/m³, 1180 ml/m³: +18%, +21%) and the relative liver weights (+19%, +29%) were increased after 12 weeks, and at 1180 ml/m³ the absolute (+15%) and relative kidney weights (+17%) after 8 weeks. Microscopic examination after 8 and 12 weeks revealed slight multifocal tubular degeneration and regeneration in the kidneys of male rats of both concentration groups. The relative adrenal weights were not consistently increased, which is therefore not regarded as a substance-related effect. Some haematocrit and haemoglobin values as well as erythrocyte counts were decreased at different times, however within the range of historical controls of the test laboratory, and were thus regarded as an expression of biological variability. The blood urea concentrations were increased in the female animals at the concentration of 385 ml/m³ after 12 weeks, but not at 1180 ml/m³; the increase was therefore not concentration-dependent. At the concentration of 1180 ml/m³, in some animals marked salivation and laboured irregular or rapid breathing were observed, and in the control animals likewise marked salivation and bleeding in the ear. In individual animals of all groups, rales, marked lacrimation, hair loss and the discharge of a reddish secretion from the eyes were found, however, there was no concentration dependency. At the concentration of 1180 ml/m³, yellow discoloration of the coat in the anogenital region was seen, which was presumably due to decreased grooming behaviour. No deaths occurred; there was no substance-related decrease in body weights (Exxon Mobil Corporation 1979 a). The isoalkane-induced changes in the kidneys of male rats are due to a α2u-globulin-dependent mechanism (Carrillo et al. 2013), which is sex-specific and species-specific and is of no relevance for humans (Swenberg 1993). From this study, a NOAEC for systemic effects of 385 ml/m³ can be derived. Because the nose and larynx were not examined, it is not possible to give a NOAEC for local effects.

The C8 hydrocarbon ***n*-octane** can also be used as a reference substance for systemic effects.

In a 13-week inhalation study in F344 rats carried out according to OECD Test Guideline 413, no effects were found up to the highest *n*-octane concentration tested of 1600 ml/m³. The NOAEC for systemic effects is therefore higher than 1600 ml *n*-octane/m³ (see Section "Local effects"; Sung et al. 2010). The liver effects typical-

ly caused by branched hydrocarbons, such as the induction of metabolizing liver enzymes and increased liver weights, are covered, as described above, by the other branched C8 alkanes.

Developmental toxicity

There are no data available for the developmental toxicity of trimethylpentane isomers.

Like in the assessment of the systemic effects, other **C8 isoalkanes** can be used as reference substances for the developmental toxicity of the substance. In the following study, the same mixture was used as that in the study of Exxon Mobil Corporation (1979 a; see Section "Systemic effects"), which consisted of about 80% to 90% 2,2,4-trimethylpentane; the total content of trimethylpentane isomers was more than 95% (Adenuga 2016).

In a segment II study in Sprague Dawley rats with inhalation exposure to C8 isoalkane concentrations of 0, 400 or 1200 ml/m^3 (whole-body, 6 hours/day) from days 6 to 15 of gestation (20 animals/group), the dams of both concentration groups were found to have a higher percentage of implantations related to the total number of corpora lutea compared with the percentage in the control group. In the high concentration group an increased incidence of foetuses with delayed ossification (variations) were found. The incidence of litters with foetuses with delayed ossification was not increased. The types of delayed ossification were similar to those found in the control group. No foetotoxic or teratogenic effects were observed up to the high concentration (Exxon Mobil Corporation 1979 b). The NOAEC for developmental and maternal toxicity was higher than 1200 ml C8 isoalkanes/m^3.

Genotoxicity and carcinogenicity

For the trimethylpentane isomers, there are no new genotoxicity studies available and no carcinogenicity studies.

Manifesto (MAK value/classification)

Carcinogenicity. Classification in Carcinogen category 3A was based on the following assumptions (supplement "Trimethylpentane (all isomers)" 2004; supplement "Trimethylpentane (all isomers)" 2006): in the mixture used, only the trimethylpentane isomers are responsible for the tumour-promoting effect of unleaded petrol, and the composition of the petrol formulations used in the carcinogenicity study in mice (Magaw et al. 1993; MacFarland et al. 1984) is similar to that used in the mechanistic studies (supplement "Trimethylpentane (all isomers)" 2004; supplement "Trimethylpentane (all isomers)" 2006).

The carcinogenicity study in B6C3F1 mice was carried out with unleaded petrol prepared in the USA according to a specification from 1976 (MacFarland et al. 1984). The mechanistic investigations were carried out in 1993 and thereafter. In

these studies, formulations of unleaded petrol (PS-6 Blend, API 91-01 Blend) were used (supplement "Trimethylpentane (all isomers)" 2004; supplement "Trimethylpentane (all isomers)" 2006). It was mentioned that PS-6 Blend originated from the same lot as that used in the carcinogenicity study (Standeven and Goldsworthy 1993) and its composition is presented in MacFarland et al. (1984). No information is available for API 91-01 Blend in this respect. Nor do the publications cited in this study provide any information about the composition; to clarify analytical questions they refer to 20 different test formulations of unleaded petrol (Gerry et al. 1992; Pahl and McNally 1990). A period of about 10 years separates the publication of the carcinogenicity study in 1984 and the mechanistic investigations. During that time, differences in the composition of the extracted crude oil and the subsequent refining and further processing developed. In addition, there is no information available for the substances used for blending, the addition of biogenic or synthetic components. The composition of the petrol formulations used in the carcinogenicity study in mice and in the mechanistic studies is therefore not assumed to be the same.

Also other unknown substances were present in the petrol used in the carcinogenicity study, as 25.8% of the petrol was not characterized analytically (MacFarland et al. 1984). Other components which could have an effect on the tumour promotion of unleaded petrol are: *tert*-butyl methyl ether and *tert*-butyl ethyl ether, aromatics like ethylbenzene, and olefins. Therefore, the petrol formulations used are no longer considered characteristic for trimethylpentane isomers.

In female B6C3F1 mice, unleaded petrol vapour has been shown to be carcinogenic to the liver (MacFarland et al. 1984; Magaw et al. 1993). In the case of the unleaded petrol, the assumed sex-specific, liver tumour-promoting effect does not explain the selective development of tumours in female B6C3F1 mice, as the liver tumour-promoting effect occurs also in male animals of this strain (Standeven et al. 1995). Therefore, it is to be assumed that also other components contribute to the tumour-promoting effect of unleaded petrol. Enzyme induction, for example, is initiated by many components of unleaded petrol and cannot be attributed to the trimethylpentane isomers alone (Standeven and Goldsworthy 1994).

To summarize: it is difficult to draw conclusions about the carcinogenicity of the individual substances of petrol from the carcinogenicity study with unleaded petrol, a mixture of more than 542 hydrocarbons (MacFarland et al. 1984), and mechanistic investigations of the trimethylpentane isomers as individual components of the petrol. Trimethylpentane isomers have therefore been removed from Carcinogen category 3A.

MAK value. The critical effect of **trimethylpentane isomers** is their acute effect on the central nervous system of rats.

The central nervous effects, rather than the local effects, are also the main effects of ***n*-octane** (documentation "Octane and its isomers (except trimethylpentane isomers)" 2004).

The NOAEC for acute neurotoxic effects from the study in rats with 60-minute inhalation exposure is 500 ml **2,2,4-trimethylpentane**/m³ (Boyes et al. 2010). This is a conservative value because at the next-higher concentration of 1000 ml/m³ the effects were still only slight.

There are no animal experiments available in which trimethylpentane concentrations in the brain were determined. As there are no studies with longer exposure durations, it is unclear how the trimethylpentane concentration develops in the organism or specifically in the brain after continued exposure over a shift of 8 hours or during long-term exposure. In the following, an attempt is made to clarify this on the basis of the hypothesis that the acute neurotoxic effect, the reduction in VEPs, is dependent on the concentration of the parent substance in the brain.

Knowledge of the half-lives of trimethylpentane isomers would make it possible to evaluate whether they accumulate in the brain during continued exposure. Trimethylpentane isomers pass the blood–brain barrier in both directions, which means that there is an equilibrium between the concentration in the brain and the concentration in blood. Accumulation in the brain due to irreversible binding of the parent substance or of trimethylpentane metabolites is not known and is also not likely.

It was shown using a PBPK model (El-Masri et al. 2009) that the increase in the concentration of modelled 2,2,4-trimethylpentane concentrations in blood decreases markedly already during the first hour—the more so, the lower the exposure level. In contrast, there is an almost linear increase in the concentration in the brain during the first hour (Boyes et al. 2010). Whether this increase—especially in the case of exposure at the level of the NOAEC of 500 ml/m^3—continues in the same way beyond the first hour is questionable in view of the development of the concentration in the blood. As the equilibrium between the blood and brain is reached relatively quickly, the increase in the concentration in the brain should slow down very rapidly already during the second hour. From this, a half-life in the brain of about one hour can be estimated. The steady state, which is reached after 5 half-lives, would thus be obtained after about 5 hours. As the steady state concentration is about twice as high as after one half-life, which is one hour, the concentration is doubled for the extrapolation of 1 hour to 8 hours.

Because of the similar toxicokinetics of *n*-alkanes and *iso*-alkanes (Zahlsen et al. 1993), experimental data from these compounds are used.

In rats, for the branched C8 alkane **2-methylheptane**, a half-life of a maximum 2 hours can be derived from the decreasing concentrations in blood and tissue, which were below the detection limit 12 hours after the end of exposure (Zahlsen et al. 1993). The half-life must, however, be shorter, since the substance was no longer detectable 12 hours after the exposure and in the meantime was not determined.

In rats exposed for 8 hours to *n*-decane concentrations of about 480 mg/m^3, a maximum 2-fold increase in the level in the brain was measured after 8 hours compared with the level determined after 2 hours. The modelled brain concentrations of *n*-decane suggest that the concentration after one hour is about as high as that after two hours. The modelled concentrations in the brain of 3 male test persons, in whom the concentrations in blood were determined, are about the same level as those determined in rats (Hissink et al. 2007).

The brain/blood partition coefficients of linear alkanes (C7 to C10; Zahlsen et al. 1992) and branched alkanes (C8: 2-methylheptane, C9: 2-methyloctane, C10: 2-methylnonane; Zahlsen et al. 1993) are between 3 and 13, that of 2,2,4-trimethylpentane is 1 (Boyes et al. 2010). This discrepancy is presumably due to the use of different analytical procedures.

To summarize, it can be assumed that the **2,2,4-trimethylpentane** concentration in the brain in the case of exposure at the level of the NOAEC will not increase to much more than double the concentration after one hour as stated in the study by Boyes et al. (2010).

Extrapolation to long-term exposure does not need to be carried out, as accumulation of the substance is not suggested by a half-life in the range of about 1 to 2 hours. This is confirmed by investigations with *n*-nonane, in which the level in the brain was not found to increase after 3, 7, 10 and 14 days in rats exposed to 1000 ml/m^3 daily for 12 hours (Zahlsen et al. 1990).

In general, organic solvents act via the reduction of glutamatergic neurotransmission and the strengthening of GABAergic neurotransmission. The molecular points of attack of the interaction of solvents, ion channels and neurotransmitter receptors have been well conserved during evolution. There is a high level of empirical evidence that the fine structures of the nervous system of rodents are very similar to those of humans (for example Albuquerque et al. 2009; Bale et al. 2005; Chiu et al. 1999). The complexity of the whole organ, however, is very different. However, based on the molecular points of attack, no great differences between humans and animals are to be expected with regard to their sensitivity to 2,2,4-trimethylpentane.

The increased respiratory volume does not need to be taken into account because the blood/air partition coefficient is lower than 5 according to the formula of Buist et al. (2012).

Assuming a maximum 2-fold increase in the 2,2,4-trimethylpentane concentration in the brain following daily 8-hour exposure and in view of the lack of reliable data and uncertainties when extrapolating these data from animal studies to humans, a MAK value of 100 ml 2,2,4-trimethylpentane/m^3 has been derived. With regard to neurotoxicity, the three other trimethylpentane isomers are assumed to have effects similar to those caused by 2,2,4-trimethylpentane. Therefore, a MAK value of 100 ml/m^3 (470 mg/m^3) has been established for all trimethylpentane isomers.

Peak limitation. The critical effect for the derivation of the MAK value is the systemic toxicity of the substance. The trimethylpentane isomers are therefore classified in Peak Limitation Category II. The half-life in the brain derived for 2,2,4-trimethylpentane is at least one hour. This is also assumed for the other trimethylpentane isomers. According to the procedures of the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (see documentation "Peak limitation: Limitation of exposure peaks and short-term exposures" 2011) an excursion factor of 2 has been established.

Prenatal toxicity. There are no data available for the developmental toxicity of the trimethylpentane isomers. The reference substances already used for the assessment of the systemic effects, the **C8 isoalkanes**, which contain about 80% to 90% 2,2,4-trimethylpentane and more than 95% trimethylpentane isomers (Adenuga 2016), were investigated in a segment II study in Sprague Dawley rats. No foetotoxic or teratogenic effects were found up to the high concentration of 1200 ml C8 isoalkanes/m^3 (Exxon Mobil Corporation 1979 b). The NOAEC for developmental toxicity and maternal toxicity is therefore higher than 1200 ml C8 isoalkanes/m^3. The MAK value of 100 ml trimethylpentane isomers/m^3 is derived from

the acute neurotoxicity in rats. Acute neurotoxic effects are to be clearly distinguished from the neurotoxic effects resulting from the developmental toxicity of the substance. It has not yet been examined what effects acute neurotoxicity has on the in utero development of the nervous system, and the risk of damage to the nervous system during development cannot be excluded with certainty. For trimethylpentane isomers and for other C8 hydrocarbons, there are no studies available for functional or behavioural end points (ontogenesis of behaviour, motor activity, motor and sensory function, learning and memory capacity), such as prescribed in OECD Test Guideline 426. Trimethylpentane isomers are therefore classified in Pregnancy Risk Group D.

Absorption through the skin. For the structural analogue *n*-heptane, the dermal absorption of 44 mg can be estimated from an in vitro study with human skin (see Section "Toxicokinetics and Metabolism") after exposure to undiluted *n*-heptane assuming the exposure of 2000 cm^2 of skin for one hour. This value is also predicted for the trimethylpentane isomers. At the level of the MAK value of 100 ml/m^3 (470 mg/m^3), 4700 mg would be absorbed assuming a respiratory volume of 10 m^3 and 100% absorption. Absorption through the skin is thus markedly below the systemically tolerable dose, and the substance is therefore not designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. For sensitization there are still no clinical findings or positive results from animal experiments available. Trimethylpentane isomers are therefore not designated with "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

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