

*The MAK Collection for Occupational Health and Safety*

## 4-tert-Octylphenol

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

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# 4-tert-Octylphenol / 4-(2,4,4-trimethyl- pentan-2-yl)phenol

## MAK Value Documentation

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### Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated the developmental toxicity of 4-tert-octylphenol. In 2015, the maximum concentration at the workplace (MAK value) for 4-tert-octylphenol was set at 0.5 ml /m<sup>3</sup> (4.3 mg/m<sup>3</sup>).

In a screening study in rats with gavage administration, litter size and body weight of the progeny at postnatal day 4 was reduced at 500 mg/kg body weight and day, accompanied by maternal toxicity. A NOAEL for foetotoxicity of 250 mg/kg body weight and day was derived, corresponding to a concentration of 28.5 ml/m<sup>3</sup> at the workplace. In a 2-generation feeding study in rats, foetotoxicity was not observed until postnatal day 13. At 111–369 mg/kg body weight and day, vaginal opening or preputial separation of the F2 progeny was delayed. A NOAEL of 10.9–32.6 mg/kg body weight and day was derived for postnatal developmental toxicity in rats, corresponding to 1.2–3.7 ml/m<sup>3</sup>. Because adequate studies of prenatal developmental toxicity over the complete period of organogenesis are lacking, data are not sufficient for classification and 4-tert-octylphenol is assigned to Pregnancy Risk Group D.

Completed: October 7, 2015

### Keywords

4-tert-octylphenol; 4-(2,4,4-trimethylpentan-2-yl)phenol; developmental toxicity; prenatal toxicity; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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# 4-*tert*-Octylphenol<sup>1)</sup>

[140-66-9]

## Supplement 2017

<b>MAK value (2015)</b>	<b>0.5 ml/m<sup>3</sup> <math>\triangleq</math> 4.3 mg/m<sup>3</sup></b>
<b>Peak limitation (2015)</b>	<b>Category I, excursion factor 1</b>
<b>Absorption through the skin</b>	–
<b>Sensitization</b>	–
<b>Carcinogenicity</b>	–
<b>Prenatal toxicity (2016)</b>	<b>Pregnancy Risk Group D</b>
<b>Germ cell mutagenicity</b>	–
<b>BAT value</b>	–

## Developmental Toxicity

In 2015, a MAK value of 0.5 ml/m<sup>3</sup> was established for 4-*tert*-octylphenol (documentation “4-*tert*-Octylphenol” 2016, available in German only). In this supplement, 4-*tert*-octylphenol is assigned to a pregnancy risk group.

4-*tert*-Octylphenol was added to the REACH Candidate List as a Substance of Very High Concern because 4-*tert*-octylphenol affects the hormone system in fish and thus impairs their development and reproduction (UBA 2011).

4-*tert*-Octylphenol is a substance that, for example, binds to the oestrogen receptor, affects spermatogenesis and oestrus in rats and mice, damages the uterus and ovaries or testes and epididymis, and disturbs the metabolism of sex hormones (documentation “4-*tert*-Octylphenol” 2016, available in German only).

## Toxic effects on prenatal development

Studies of toxic effects on prenatal development are listed in Table 1.

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1) The substance can occur simultaneously as a vapour and aerosol.

**Table 1** Studies of toxic effects on prenatal development after repeated exposure to 4-tert-octylphenol

Species, strain, number per group	Exposure	Findings	References
<b>rats,</b> Wistar, 16 ♀ at 0–125 mg/kg body weight, 6–7 ♀ at 250–500 mg/ kg body weight	<b>GD 0–8,</b> 0, 15.6, 31.3, 62.5, 125, 250 or 500 mg 4-tert-octylphe- nol/kg body weight and day, vehicle: olive oil, gavage, examination: GD 20	<b>15.6 mg/kg body weight and above:</b> dams: LOAEL, feed consumption ↓; foetuses: NOAEL foetotoxicity; <b>31.3 mg/kg body weight and above:</b> dams: body weight gains ↓; foetuses: post-implantation losses/litter ↑; <b>31.3 mg/kg body weight:</b> foetuses: number of live offspring/litter ↓; <b>62.5 mg/kg body weight and above:</b> dams: diarrhoea, loss of hair; <b>125 mg/kg body weight:</b> foetuses: 1 total resorption, number of live offspring/litter ↓; <b>250 mg/kg body weight:</b> dams: mortality 2/6; <b>500 mg/kg body weight:</b> dams: mortality 7/7; no external malformations or malformations of the oral cavity; no other examination of teratogenic effects	Harazono and Ema 2001
<b>rat,</b> Wistar, 8 ♀	<b>GD 1–20,</b> 0, 100 or 250 mg 4-tert-oc- tylphenol/kg body weight and day, vehicle: corn oil:ethanol (14:1), subcutaneous, purity: 97%, weaning of F1 at 1 month of age, examination of F1 at 2.5 months of age	<b>100 mg/kg body weight and above:</b> F1 ♀: erythrocyte count ↓, liver: fatty deposits, degeneration of the parenchyma, spleen: haemosiderin deposits; F1 ♂: liver: fatty deposits; infiltration of inflammatory cells, congestion, F1 ♀ and ♂: kidneys: infiltration of inflammatory cells, congestion, tubular degenera- tion, spleen: haemorrhages, fibrosis, extramedullary haematopoiesis, lipidosis; <b>250 mg/kg body weight:</b> F1 ♀ and ♂: blood and platelet count ↓, MCV ↓, F1 ♂: haemoglobin and haematocrit values ↓, liver: degeneration of the parenchyma, spleen: haemosiderin deposits; no maternal toxicity	Barlas and Aydoğan 2009

Table 1 (continued)

Species, strain, number per group	Exposure	Findings	References
<b>rat</b> , Sprague Dawley, 5 ♀	<b>GD 13, 15 and 17</b> , 0, 0.1, 10 or 100 mg 4- <i>tert</i> -octylphenol/kg body weight and day, vehicle: corn oil, sub- cutaneous, purity: 97%	<b>100 mg/kg body weight</b> : no significant effects on body weights or testosterone concentration in testes	Haavisto et al. 2003
<b>mouse</b> , NMRL, 8 ♀	<b>GD 11–16</b> , 0, 1 or 250 mg 4- <i>tert</i> -octyl- phenol/kg body weight and day, vehicle: arachis oil, subcutaneous, purity: 97%, examination of F1 ♀: immediately after birth	<b>up to 250 mg/kg body weight</b> : FI: no effects on survival, number of oocytes or percentage distribution of prefollicular, follicular or atretic oocytes	Sonne-Hansen et al. 2003
<b>rabbit</b> , Dutch Belted, 4–6 ♀	<b>GD 15–30</b> , 0 or 150 mg 4- <i>tert</i> -octyl- phenol/kg body weight and day, on alternate days, vehicle: corn syrup, subcutaneous, examination of F1: at 24–26 weeks of age	<b>150 mg/kg body weight</b> : offspring: unilateral testicular dystrophy, one of these testes with atypical germ cells (1/4 F1); authors: atypical germ cells substance-induced, not related to the undescended testes	Veeramachaneni 2006

Table 1 (continued)

Species, strain, number per group	Exposure	Findings	References
<b>sheep</b> , Suffolk Cross, ♀ no other details	<b>GD 110–115</b> , 0 or 1 mg 4-tert-octylphenol/kg body weight and day; vehicle: alcohol:saline (1:4), continuous intravenous infusion, purity: 97%	<b>1 mg/kg body weight:</b> dams: FSH concentration ↑, no significant changes in LH concentration; no other examinations	Sweeney et al. 2000
<b>sheep</b> , Suffolk Cross, ♀ no other details	<b>GD 70 to birth</b> 0 or 1 mg 4-tert-octylphenol/kg body weight and day, 2x/week, vehicle: corn oil, subcutaneous, purity: 97%, examination: immediately after birth	<b>1 mg/kg body weight:</b> dams: FSH mRNA ↓, foetuses: pituitary: number of FSH-immunopositive cells ↓, testis: weights and number of Sertoli cells ↓	Sweeney et al. 2000
<b>pig</b> , not specified, 14 ♀	<b>GD 20–24</b> , 0, 0.1 or 1.0 mg 4-tert-octylphenol/kg body weight and day, purity: 97%, vehicle: corn oil, intramuscular, examination: immediately after birth	<b>1 mg/kg body weight:</b> piglets: stillbirths ↑; ♂ piglets: no effects found in the gross-pathological examination or on the testosterone concentration in serum	Gralén et al. 2012

GD = gestation day; FSH = follicle-stimulating hormone; LH = luteinizing hormone; MCV = mean corpuscular volume

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After oral administration of 4-*tert*-octylphenol to Wistar rats, a NOAEL (no observed adverse effect level) for foetotoxic effects of 15.6 mg/kg body weight and day and a LOAEL (lowest observed adverse effect level) of 31 mg/kg body weight and day were derived for early prenatal development from the time of mating to gestation day 8 (Harazono and Ema 2001). However, the study did not cover the period up to gestation day 15 that is required for the examination of toxic effects on prenatal development. Likewise, a full evaluation of the teratogenic effects was not possible because only external malformations were recorded.

The effects observed in rats or mice after intraperitoneal exposure (Sainath et al. 2011) are not included in the evaluation because the form of administration may have had a direct effect on the foetuses and these studies are therefore not relevant to exposure at the workplace. Likewise, the studies in rabbits with subcutaneous injection on alternate days (Veeramachaneni 2006) and also in sheep (Sweeney et al. 2000) and pigs (Gralén et al. 2012) are not considered because there are no adequate reference values or standardized methods available for this type of administration or these animal species.

### Screening and generation studies

The results of the screening and generation studies are listed in Table 2.

In a screening study in rats that were given gavage doses of 4-*tert*-octylphenol, initial effects on the foetuses were observed together with maternal toxicity at 500 mg/kg body weight and day and above. The NOAEL for foetotoxicity was 250 mg/kg body weight and day (Sandoz Chemicals Ltd 1995).

In a 2-generation study in rats given 4-*tert*-octylphenol with the diet, the time of vaginal opening or preputial separation was delayed in the F2 offspring at the high dose of 111 to 369 mg/kg body weight and day. At the same time, maternal toxicity was observed in the form of reduced body weights or reduced body weight gains. No adverse effects on the litter parameters or reproductive organs of male offspring were detected up to postnatal day 13. The body weight gains in the offspring were decreased at 111 to 369 mg/kg body weight and day on postnatal day 14 and thereafter. The NOAEL for toxic effects on postnatal development and maternal toxicity was 10.9 to 32.6 mg 4-*tert*-octylphenol/kg body weight and day (Tyl et al. 1999).

A 3-generation study in rats, which included the treatment of pups, examined only effects on the liver (Hernández-Rodríguez et al. 2007). Effects that are induced by the treatment of pups are not suitable for evaluating the adverse effects on health of 4-*tert*-octylphenol at the workplace.

After the subcutaneous treatment of sows with 4-*tert*-octylphenol during gestation, the onset of puberty was accelerated in the female offspring at 10 mg/kg body weight and day and above, and the litter size of the F2 generation was reduced at 100 mg/kg body weight and day (Bøgh et al. 2001). The results are not included in the evaluation because there are no adequate reference values or standardized methods available for this animal species.

**Table 2** Screening and generation studies of toxic effects of 4-tert-octylphenol on prenatal and postnatal development

Species, strain, number per group	Exposure	Findings	References
<b>screening studies</b>			
<b>rat</b> , Wistar; 4 ♂, 4 ♀, age: 12–15 weeks	<b>screening study</b> 41 days, 0 or 100 mg 4-tert-octylphenol/kg body weight and day, purity: ≥ 90%, 14 days before mating, during gestation, up to PND 6, daily, vehicle: corn oil, gavage, OECD Test Guideline 421 with a reduced number of animals	<b>100 mg/kg body weight:</b> feed consumption and body weight gains ↓, 2/4 ♀ pregnant; no unusual findings in the histological examination, no change in testis weights, no significant effects on number of corpora lutea, concentrations of oestradiol, progesterone, testosterone, LH or FSH	Piersma et al. 1998

Table 2 (continued)

Species, strain, number per group	Exposure	Findings	References
<b>rat.</b> Sprague Dawley, 12 ♂, 12 ♀	<b>screening study,</b> <b>39 days</b> 0, 125, 250 or 500 mg 4- <i>tert</i> -octylphenol/kg body weight and day, daily, vehicle: corn oil, gavage, purity: 98.7% beginning: 14 days before mating, during gestation, up to PND 4, OECD Test Guideline 421	<b>125 mg/kg body weight and above:</b> parental animals: salivation immediately after administration of the test substance, <b>NOAEL for maternal toxicity</b> ; <b>250 mg/kg body weight and above:</b> parental animals: body weight gains ↓, water consumption ↑, size of the adrenal glands ↑; offspring: <b>NOAEL for foetotoxicity</b> ; <b>500 mg/kg body weight:</b> parental animals: ♀: feed consumption ↓, mortality (13/24, of these 9 ♂ and 4 ♀), reddish brown discoloration around the snouts immediately after administration of the test substance, ruffled and matted fur, hunched posture, abnormal gait, emaciation, lethargy, blood: ♂: leukocytes and platelets ↑, ALT, urea nitrogen, creatinine and bilirubin ↑ and change in electrolytes, weights of sex organs and thymus ↓; gross pathology: ♀: stomach: thickened areas and foci, enlarged lymph nodes; offspring: implantations ↓, litter size (because of prenatal and postnatal mortality on PND 0 and 4) ↓, average litter weights ↓, delayed growth up to PND 4	Sandoz Chemicals Ltd 1995; OECD 1994
<b>generation studies</b>	<b>2-generation study,</b> 0, 0.2, 20, 200 or 2000 mg 4- <i>tert</i> -octylphenol/kg diet (0, 0.011–0.034, 1.05–3.3, 10.9–32.6, 111–369 mg/kg body weight and day), purity: about 90.2%, F0 and F1: 10 weeks before mating, during gestation, up to weaning of the offspring on PND 21	<b>10.9–32.6 mg/kg body weight:</b> parental animals: <b>NOAEL for maternal toxicity</b> ; offspring: <b>NOAEL for developmental toxicity</b> ; <b>111–369 mg/kg body weight:</b> parental animals: ♀: absolute and relative uterus weights ↓ (only F0; not substance-induced because not found in F1); body weights and body weight gains ↓: terminal body weights: F0 ♂ 7.3% ↓, F1 ♂ 9.3% ↓ and F2 ♂ 7.4% ↓; F1 ♀: before mating, during gestation and lactation: body weights ↓, but terminal body weights no longer significantly decreased; offspring: body weights ↓ (F1: PND 14, 21; F2: PND 21), delayed vaginal opening or preputial separation (only F2 examined); anogenital distance increased (PND 0; only F2 ♀), no effects on litter parameters or male reproductive organs of the offspring up to PND 13	Tyl et al. 1999

Table 2 (continued)

Species, strain, number per group	Exposure	Findings	References
<b>rat</b> , Sprague Dawley, F0: 2 ♂, 2 ♀, F1-F3: 10 ♂, 10 ♀	<b>3-generation study</b> , 0 or 25 mg 4-tert-octylphenol/l drinking water (about 0 or 2 mg/kg body weight and day), F0: beginning: at 3 weeks of age, during mating at 3 months of age and during gestation, up to weaning of the pups, F1, F2 or F3: about 10 ♂ and 10 ♀, beginning: at the age of 3 months, exposure about 6 months: during mating and gestation, up to weaning of the pups	<b>2 mg/kg body weight:</b> liver: hepatocytes: apoptotic index ↑, % binuclear hepatocytes ↑, disturbance in glucose homeostasis, no abnormalities in relative weights or structure; only liver examined in F1, F2 and F3 pups; effects induced by the treatment of pups are not suitable for the evaluation of adverse effects of 4-tert-octylphenol on health at the workplace	Hernández-Rodríguez et al. 2007
<b>pig</b> , Landrace x Yorkshire, 13 ♀	<b>3-generation study</b> , 0, 10 or 1000 mg 4-tert-octylphenol/kg body weight and day, gestation day 23–85, daily, subcutaneous	<b>10 mg/kg body weight and above:</b> F0: prolonged gestation, basal cell proliferation in the cervical epithelium; F1 female offspring: accelerated onset of puberty; <b>100 mg/kg body weight:</b> mating of F1 ♀ with F1 ♂ originating from dams treated with high doses: litter size ↓; no unusual findings for body weight gains, in the gross-pathological examination of the genitals of F1 and F2, for testis development during puberty or in the examination of the sperm: volume, morphology and motility, concentration and live sperm (only F1 examined)	Bøgh et al. 2001

ALT = alanine aminotransferase; FSH = follicle-stimulating hormone; LH = luteinizing hormone; PND = postnatal day

### Toxic effects on postnatal development

The effects on sex organs or other organs observed in the offspring of rats and mice after postnatal oral, subcutaneous or intraperitoneal treatment with 4-*tert*-octylphenol (An et al. 2013; Atanassova et al. 2000; Aydođan and Barlas 2006; Bicknell et al. 1995; Blake and Ashiru 1997; Fisher et al. 1999; Göktekin and Barlas 2008; Götz et al. 2001; Herath et al. 2001; Kamei et al. 2008; Katsuda et al. 2000; Mikkilä et al. 2006; Myllymäki et al. 2005; Nagao et al. 2001; Pocock et al. 2002; vom Saal et al. 1998; Sharpe et al. 1995, 1998, 2003; Williams et al. 2001; Willoughby et al. 2005; Yoshida et al. 2001, 2002 a, b) are not included in the evaluation because these studies are not relevant to exposure at the workplace and there may be direct effects on the foetuses after intraperitoneal injection.

It is assumed that exposure to 4-*tert*-octylphenol during gestation may lead to hyperactivity in the offspring (Masuo et al. 2004; Christian and Gillies 1999). The results of motor hyperactivity are not considered in the evaluation of toxic effects on postnatal development because studies with intracisternal administration are not relevant to exposure at the workplace.

#### Summary

Based on the post-implantation losses that were observed at 31.3 mg/kg body weight and day and above, a NOAEL for foetotoxicity of 15 mg 4-*tert*-octylphenol/kg body weight and day was derived from the available studies for early prenatal developmental toxicity in Wistar rats up to gestation day 8. A full examination of the teratogenic effects was not carried out (Harazono and Ema 2001). There are no studies available with exposure to 4-*tert*-octylphenol up to gestation day 15 (rats) or 19 (rabbits) that were carried out in conformity with test guidelines.

A screening study in rats that were given gavage doses of 4-*tert*-octylphenol revealed initial effects on the foetuses together with maternal toxicity at 500 mg/kg body weight and day and above. The NOAEL was 250 mg/kg body weight and day (Sandoz Chemicals Ltd 1995). The screening study relativizes the findings obtained in the study with treatment of rats from mating to gestation day 8 because the screening study did not reveal any effects on the offspring after treatment throughout gestation.

In a 2-generation study with rats given 4-*tert*-octylphenol with the diet, reduced body weight gains and delayed vaginal opening or preputial separation were observed in the F2 offspring together with maternal toxicity at the high dose of 111 to 369 mg/kg body weight and day on postnatal day 14 and thereafter. The NOAEL for toxic effects on postnatal development and maternal toxicity was 10.9 to 32.6 mg 4-*tert*-octylphenol/kg body weight and day (Tyl et al. 1999).

### Manifesto (Developmental Toxicity)

**Prenatal toxicity.** In the only study of the toxic effects of 4-*tert*-octylphenol on prenatal development with a restricted duration of treatment up to gestation day 8, the number of post-implantation losses per litter was increased and the number of live offspring therefore reduced in Wistar rats at 31.3 mg/kg body weight and day

and above. This dose also caused maternal toxicity. A full evaluation of the teratogenic effects was not carried out (Harazono and Ema 2001). In a screening study carried out in Sprague Dawley rats with 4-*tert*-octylphenol according to OECD Test Guideline 421, the litter size and the body weights of the offspring were reduced and maternal toxicity was observed on postnatal day 4 at 500 mg/kg body weight and day. The NOAEL for foetotoxicity was 250 mg/kg body weight and day (Sandoz Chemicals Ltd 1995) and relativizes the finding of post-implantation losses. In the 2-generation study, foetotoxicity was not observed up to postnatal day 13, but the time of vaginal opening or preputial separation was delayed at 111 to 369 mg/kg body weight and day. The NOAEL for toxic effects on postnatal development was thus 10.9 to 32.6 mg/kg body weight and day (Tyl et al. 1999).

The following toxicokinetic data are used to extrapolate the NOAEL for foetotoxicity of 250 mg 4-*tert*-octylphenol/kg body weight and day and the NOAEL for toxic effects on postnatal development of 10.9 to 32.6 mg/kg body weight and day in rats to a concentration in workplace air: the daily exposure of the animals in comparison with the exposure for 5 days per week at the workplace (7:5), the corresponding species-specific correction value for the rat determined on the basis of the toxicokinetic data (1:4), the ratio of the effects of inhalation exposure to those of the oral dose of 0.4 (see documentation "4-*tert*-Octylphenol" 2016, available in German only), the body weight (70 kg) and the respiratory volume (10 m<sup>3</sup>) of the person, and the assumed 100% absorption by inhalation. The resulting concentrations of 245 and 10.7 to 31.8 mg/m<sup>3</sup> (28.5 and 1.2 to 3.7 ml/m<sup>3</sup>) are 57 times higher and 3 to 8 times higher than the MAK value of 0.5 ml/m<sup>3</sup> (4.3 mg/m<sup>3</sup>).

With no adequate studies of toxic effects on prenatal development available and a full evaluation of teratogenicity still outstanding, 4-*tert*-octylphenol is classified in Pregnancy Risk Group D.

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