Health Based Guidance for Water
Health Risk Assessment Unit, Environmental Health Division
651-201-4899

Adopted as Rule: November 2023

Toxicological Summary for: 4-*tert*-Octylphenol

CAS: **140-66-9**

Synonyms: 4-(1,1,3,3-Tetramethylbutyl)phenol, *p*-(1,1,3,3-Tetramethylbutyl)phenol, *p-tert*-Octylphenol, 4-(2,4,4-trimethylpentan-2-yl)phenol

Acute Non-Cancer Health Risk Limit (nHRLAcute) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Risk Limit (nHRLShort-term) = 100 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Short-term Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.17 mg/kg-d) x (0.2*) x (1000 µg/mg)}}{\text{(0.290 L/kg-d)**}}$$

= 117 rounded to **100 µg/L**

*The available data indicate that infant exposures, from sources such as breast milk and baby food, are not lower than adult exposures. As infant exposures are equal to or exceed adult exposures based on the available exposure data, a relative source contribution of 0.2 has been selected for all durations.

** Intake rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 5.06/30 = 0.17 mg/kg-d (Sprague-Dawley rats)
Source of toxicity value:	Determined by MDH in 2015
Point of Departure (POD):	22 mg/kg-d (administered dose NOAEL, 2-generation reproductive study, Tyl *et al.* 1999)
Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (US EPA 2011, MDH 2017)
Human Equivalent Dose (HED):	POD X DAF = 22 mg/kg-d x 0.23 = 5.06 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics) and 10 for intraspecies variability
Critical effect(s):	Decreased pup body weight and increased time to preputial separation
Co-critical effect(s):	Decreased adult body weight
Additivity endpoint(s):	Developmental

Subchronic Non-Cancer Health Risk Limit ($nHRL_{Subchronic}$) = $nHRL_{Short\text{-}term}$ = 100 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.17 mg/kg-d) x (0.2) x (1000 µg/mg)}}{\text{(0.074 L/kg-d)**}}$$

= 459 rounded to 500 µg/L

** Intake rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 5.06/30 = 0.17 mg/kg-d (Sprague-Dawley rats)
Source of toxicity value:	Determined by MDH in 2015
Point of Departure (POD):	22 mg/kg-d (administered dose NOAEL, 2-generation reproductive study, Tyl *et al.* 1999)
Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (US EPA 2011, MDH 2017)
Human Equivalent Dose (HED):	POD X DAF = 22 mg/kg-d x 0.23 = 5.06 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics) and 10 for intraspecies variability
Critical effect(s):	Decreased uterine weight
Co-critical effect(s):	Decreased adult body weight
Additivity endpoint(s):	Female Reproductive system

The Subchronic nHRL must be protective of the short-term exposures that occur within the subchronic period and therefore, the Subchronic nHRL is set equal to the Short-term nHRL of 100 µg/L. Additivity endpoints: Developmental

Chronic Non-Cancer Health Risk Limit ($nHRL_{Chronic}$) = $nHRL_{Short\text{-}term}$ = 100 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.051 mg/kg-d) x (0.2) x (1000 µg/mg)}}{\text{(0.045 L/kg-d)**}}$$

= 226 rounded to 200 µg/L

** Intake rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 5.06/100 = 0.051 mg/kg-d (Sprague-Dawley rats)
Source of toxicity value:	Determined by MDH in 2015
Point of Departure (POD):	22 mg/kg-d (administered dose NOAEL, 2-generation reproductive study, Tyl *et al.* 1999, subchronic exposure)
Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (US EPA 2011, MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 22 mg/kg-d x 0.23 = 5.06 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for subchronic to chronic extrapolation
Critical effect(s):	Decreased uterine weight
Co-critical effect(s):	Decreased adult body weight
Additivity endpoint(s):	Female Reproductive system

The Chronic nHRL must be protective of the short-term and subchronic exposures that occur within the chronic period and therefore, the Chronic nHRL is set equal to the Short-term nHRL of 100 µg/L. Additivity endpoints: Developmental

Cancer Health Risk Limit (cHRL) = **Not Applicable**

Volatile: Yes (low)

Summary of Guidance Value History:
An HBV of 100 µg/L for all durations was developed in 2015. In 2020, MDH re-evaluated 4-tert-octylphenol resulting in no changes to the guidance value, however, the recent detections of 4-tert-octylphenol in Minnesota groundwater made it eligible for rule. Also in 2020, MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values. In November 2023, the guidance values were adopted into Minnesota Rules, 4717.7860, as Health Risk Limits (HRLs).

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):
Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	Yes	No	Yes	Yes	Yes
Effects observed?	Yes[1]	--[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:
[1]Endocrine effects such as increased uterine weights, increased vaginal and uterine thickness, and

changes in estrus cyclicity were reported in female rats receiving doses approximately 35-275 times higher than the short-term RfD. In addition, male animals receiving doses approximately 225 times higher than the short-term RfD had increased prolactin levels.

[2] No oral studies specifically evaluating immunotoxicity have been conducted. Studies examining other endpoints reported reduced thymus and spleen weights at approximately 300 times higher than the short-term RfD, and increased white blood cell/platelet counts around 650-700 times higher than the short-term RfD.

[3]The short-term RfD is based on reduced pup body weights and delayed preputial separation after rats were exposed to 4-*tert*-Octylphenol through their diet. Precocious vaginal patency was observed at doses more than 250 times the short-term RfD.

[4]The subchronic and chronic reference doses are based on reduced uterine weights of rats exposed to 4-*tert*-Octylphenol through their diet. In other studies, doses more than 650 times higher than the short-term RfD resulted in changes in epididymis and prostate weights. In addition, an increase in post-implantation loss and the reduction of number of live fetuses per litter were observed at doses 41-160 times higher than the short-term RfD.

[5]Neurobehavioral effects, including effects on a variety of sexually dimorphic behaviors and water maze performance, were evaluated in a single oral study. The effects occurred at an estimated dose approximately 150 times higher than the short-term RfD.

Resources Consulted During Review:

Anderson, P., Denslow, N., Drewes, J. E., Olivieri, A., Schlenk, D., & Snyder, S. (2010). Final Report: Monitoring Strategies for Chemicals of Emerging Concern (CECs) in Recycled Water, Recommendations of a Science Advisory Panel.

Australian Environment Protection and Heritage Council, Australian National Health and Medical Research Council, & Australian Natural Resource Management Ministerial Council. (2008). Australian Guidelines for Water Recycling: Managing Health and Environmental Risks (Phase 2), Augmentation of Drinking Water Supplies. Retrieved from: https://www.waterquality.gov.au/sites/default/files/documents/water-recycling-guidelines-augmentation-drinking-22.pdf

Barber, L. B., Loyo-Rosales, J. E., Rice, C. P., Minarik, T. A., & Oskouie, A. K. (2015). Endocrine disrupting alkylphenolic chemicals and other contaminants in wastewater treatment plant effluents, urban streams, and fish in the Great Lakes and Upper Mississippi River Regions. *Sci Total Environ, 517C*, 195-206.

Bian, Q., Qian, J., Xu, L., Chen, J., Song, L., & Wang, X. (2006). The toxic effects of 4-tert-octylphenol on the reproductive system of male rats. *Food Chem Toxicol, 44*(8), 1355-1361.

Blake, C. A., Boockfor, F. R., Nair-Menon, J. U., Millette, C. F., Raychoudhury, S. S., & McCoy, G. L. (2004). Effects of 4-tert-octylphenol given in drinking water for 4 months on the male reproductive system of Fischer 344 rats. *Reprod Toxicol, 18*(1), 43-51.

Calafat, A. M., Ye, X., Wong, L. Y., Reidy, J. A., & Needham, L. L. (2008). Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003-2004. *Environ Health Perspect, 116*(1), 39-44.

Certa, H., Fedtke, N., Wiegand, H. J., Muller, A. M., & Bolt, H. M. (1996). Toxicokinetics of p-tert-octylphenol in male Wistar rats. *Arch Toxicol, 71*(1-2), 112-122.

Chalubinski, M., & Kowalski, M. L. (2006). Endocrine disrupters--potential modulators of the immune system and allergic response. *Allergy, 61*(11), 1326-1335.

ChemIDplus. 4-(1,1,3,3-Tetramethylbutyl)phenol. *TOXNET.* From https://chem.nlm.nih.gov/chemidplus/rn/140-66-9

Diel, P., Schmidt, S., Vollmer, G., Janning, P., Upmeier, A., Michna, H., . . . Degen, G. H. (2004). Comparative responses of three rat strains (DA/Han, Sprague-Dawley and Wistar) to treatment with environmental estrogens. *Arch Toxicol, 78*(4), 183-193.

European Chemicals Agency. (2011). Annex XV Dossier including Member state committee support document for indentification of 4-(1,1,3,3-tetramethylbutyl)phenol, 4-tert-octylphenol). Retrieved from: http://echa.europa.eu/documents/10162/397abe32-ecb8-451c-87d2-33af413687dd

Gregory, M., Lacroix, A., Haddad, S., Devine, P., Charbonneau, M., Tardif, R., . . . Cyr, D. G. (2009). Effects of chronic exposure to octylphenol on the male rat reproductive system. *J Toxicol Environ Health A, 72*(23), 1553-1560.

Hamelin, G., Charest-Tardif, G., Krishnan, K., Cyr, D., Charbonneau, M., Devine, P. J., . . . Tardif, R. (2009). Toxicokinetics of p-tert-octylphenol in male and female Sprague-Dawley rats after intravenous, oral, or subcutaneous exposures. *J Toxicol Environ Health A, 72*(8), 541-550.

Hamelin, G., Charest-Tardif, G., Krishnan, K., Cyr, D. G., Charbonneau, M., Devine, P. J., . . . Tardif, R. (2008). Determination of p-tert-octylphenol in blood and tissues by gas chromatography coupled with mass spectrometry. *J Anal Toxicol, 32*(4), 303-307.

Hanioka, N., Jinno, H., Chung, Y. S., Nishimura, T., Tanaka-Kagawa, T., & Ando, M. (2000). Effect of 4-tert-octylphenol on cytochrome P450 enzymes in rat liver. *Arch Toxicol, 73*(12), 625-631.

Harazono, A., & Ema, M. (2001). Effects of 4-tert-octylphenol on initiation and maintenance of pregnancy following oral administration during early pregnancy in rats. *Toxicol Lett, 119*(1), 79-84.

Hejmej, A., Kotula-Balak, M., Galas, J., & Bilinska, B. (2011). Effects of 4-tert-octylphenol on the testes and seminal vesicles in adult male bank voles. *Reprod Toxicol, 31*(1), 95-105.

Hossaini, A., Dalgaard, M., Vinggaard, A. M., Pakarinen, P., & Larsen, J. J. (2003). Male reproductive effects of octylphenol and estradiol in Fischer and Wistar rats. *Reprod Toxicol, 17*(5), 607-615.

ICI Americas Inc. (1996). Screening of Chemicals for Uterine Growth in Immature Female Rats: Nonylphenol, Octylphenol, and Nonylphenoxyacetic Acid: EPA TSCA Test Submission 8EHQ-0596-13647

Kamei, S., Miyawaki, J., Sakayama, K., Yamamoto, H., & Masuno, H. (2008). Perinatal and postnatal exposure to 4-tert-octylphenol inhibits cortical bone growth in width at the diaphysis in female mice. *Toxicology, 252*(1-3), 99-104.

Kim, J., Kang, E. J., Park, M. N., Lee, J. E., Hong, S. H., An, S. M., . . . An, B. S. (2014). Adverse effects of 4-tert-octylphenol on the production of oxytocin and hCG in pregnant rats. *Lab Anim Res, 30*(3), 123-130.

Kuklenyik, Z., Ekong, J., Cutchins, C. D., Needham, L. L., & Calafat, A. M. (2003). Simultaneous measurement of urinary bisphenol A and alkylphenols by automated solid-phase extractive derivatization gas chromatography/mass spectrometry. *Anal Chem, 75*(24), 6820-6825.

Laws, S. C., Carey, S. A., Ferrell, J. M., Bodman, G. J., & Cooper, R. L. (2000). Estrogenic activity of octylphenol, nonylphenol, bisphenol A and methoxychlor in rats. *Toxicol Sci, 54*(1), 154-167.

Lee, H. R., & Choi, K. C. (2013). 4-tert-Octylphenol stimulates the expression of cathepsins in human breast cancer cells and xenografted breast tumors of a mouse model via an estrogen receptor-mediated signaling pathway. *Toxicology, 304*, 13-20.

Lee, M. H., Kim, E., & Kim, T. S. (2004). Exposure to 4-tert-octylphenol, an environmentally persistent alkylphenol, enhances interleukin-4 production in T cells via NF-AT activation. *Toxicol Appl Pharmacol, 197*(1), 19-28.

Minnesota Department of Health (MDH). (2008). Statement of Need and Reasonableness (SONAR), July 11, 2008. https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH). (2011). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses. From https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

Murono, E. P., Derk, R. C., & de Leon, J. H. (2000). Octylphenol inhibits testosterone biosynthesis by cultured precursor and immature Leydig cells from rat testes. *Reprod Toxicol, 14*(3), 275-288.

Nagao, T., Yoshimura, S., Saito, Y., Nakagomi, M., Usumi, K., & Ono, H. (2001). Reproductive effects in male and female rats from neonatal exposure to p-octylphenol. *Reprod Toxicol, 15*(6), 683-692.

Organisation for Economic Co-operation and Development, U. N. E. P. (1995). Phenol, 4-(1,1,3,3-tetramethylbutyl)- Screening Information Data Sets Initial Assessment Report.

Paris, F., Balaguer, P., Terouanne, B., Servant, N., Lacoste, C., Cravedi, J. P., . . . Sultan, C. (2002). Phenylphenols, biphenols, bisphenol-A and 4-tert-octylphenol exhibit alpha and beta estrogen activities and antiandrogen activity in reporter cell lines. *Mol Cell Endocrinol, 193*(1-2), 43-49.

Petroleum Additives Panel, H., Environmental and Regulatory Task Group,. (2006). Group 28 - Phenol, Heptyl Derivatives.

Pocock, V. J., Sales, G. D., Wilson, C. A., & Milligan, S. R. (2002). Effects of perinatal octylphenol on ultrasound vocalization, behavior and reproductive physiology in rats. *Physiol Behav, 76*(4-5), 645-653.

Qin, Y., Chen, M., Wu, W., Xu, B., Tang, R., Chen, X., . . . Wang, X. (2013). Interactions between urinary 4-tert-octylphenol levels and metabolism enzyme gene variants on idiopathic male infertility. *PLoS One, 8*(3), e59398.

Sahambi, S. K., Pelland, A., Cooke, G. M., Schrader, T., Tardif, R., Charbonneau, M., . . . Devine, P. J. (2010). Oral p-tert-octylphenol exposures induce minimal toxic or estrogenic effects in adult female Sprague-Dawley rats. *J Toxicol Environ Health A, 73*(9), 607-622.

Schenectady International for U.S. EPA. (2002). Alkylphenols Category, Section Two, Ortho-substituted Mono-alkylphenols, Chemical Right-to-Know Initiative, HPV Challenge Program.

Shalaby, K. F. W., L.F.; El-Sisi, S.F.I. (2011). The Possible Toxic Effect of 4-tert-octylphenol-Polluted Water, on Male Reproductive Hormone of Rat. *Nature and Science, 9*(11), 97-107.

Sharpe, R. M., Fisher, J. S., Millar, M. M., Jobling, S., & Sumpter, J. P. (1995). Gestational and lactational exposure of rats to xenoestrogens results in reduced testicular size and sperm production. *Environ Health Perspect, 103*(12), 1136-1143.

Snyder, S. A., Bruce, G. M., & Drewes, J. E. (2010). Identifying Hormonally Active Compounds, Pharmaceuticals, and Personal Care Product Ingredients of Heatlth Concern from Potential Presence in Water Intended for Indirect Potable Reuse. Retrieved from: https://watereuse.org/download/identifying-hormonally-active-compounds-pharmaceuticals-and-personal-care-product-ingredients-of-health-concern-from-potential-presence-in-water-intended-for-indirect-potable-reuse/

Snyder, S. A., Trenholm, R. A., Snyder, E. M., Bruce, G. M., Pleus, R. C., & Hemming, J. D. C. (2008). Toxicological Relevance of EDCs and Pharmaceuticals in Drinking Water.

Suberg H., L. E., and Kaliner, G. (1982). Isooctylphenol: Subchronic Toxicological Experiments with Rats. Wuppertal, Germany: Bayer AG Institute for Toxicology.

Tyl, R. W., Myers, C. B., Marr, M. C., Brine, D. R., Fail, P. A., Seely, J. C., & Van Miller, J. P. (1999). Two-generation reproduction study with para-tert-octylphenol in rats. *Regul Toxicol Pharmacol, 30*(2 Pt 1), 81-95.

U.S. Environmental Protection Agency - Office of Research and Development. (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. From http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. Environmental Protection Agency - Office of the Science Advisor. (2011). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose.

U.S. Environmental Protection Agency. (2009). Screening-Level Hazard Characterization, Alkylphenols Category.

U.S. Environmental Protection Agency. (2010). Alkylphenol Ethoxylates (APEs-JITF CST 5 inert Ingredients). Revised Human Health Risk Assessment to Support Propsed Exemption from the Requirement of a Tolerance When Used as Inert Ingredients in Pesticide Formulations. Washington, D.C. From http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0890-0004

U.S. Environmental Protection Agency. (2019). Exposure Factors Handbook Chapter 3 Update 2019. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

United Nations Environment Programme (UNEP). (1995). 4-(1, 1, 3, 3-Tetramethyl butyl)-Phenol: SIDS Initial Assessment Report for SIAM 3.

United States Geological Survey. (2014). Health-Based Screening Levels for Evaluating Water-Quality Data. From http://cida.usgs.gov/hbsl/apex/f?p=104:1:

Upmeier, A., Degen, G. H., Schuhmacher, U. S., Certa, H., & Bolt, H. M. (1999). Toxicokinetics of p-tert-octylphenol in female DA/Han rats after single i.v. and oral application. *Arch Toxicol, 73*(4-5), 217-222.

vom Saal, F. S., Cooke, P. S., Buchanan, D. L., Palanza, P., Thayer, K. A., Nagel, S. C., . . . Welshons, W. V. (1998). A physiologically based approach to the study of bisphenol A and other estrogenic chemicals on the size of reproductive organs, daily sperm production, and behavior. *Toxicol Ind Health, 14*(1-2), 239-260.

White, R., Jobling, S., Hoare, S. A., Sumpter, J. P., & Parker, M. G. (1994). Environmentally persistent alkylphenolic compounds are estrogenic. *Endocrinology, 135*(1), 175-182.

Ye, X., Kuklenyik, Z., Needham, L. L., & Calafat, A. M. (2006). Measuring environmental phenols and chlorinated organic chemicals in breast milk using automated on-line column-switching-high performance liquid chromatography-isotope dilution tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci, 831*(1-2), 110-115.

Yon, J. M., Kwak, D. H., Cho, Y. K., Lee, S. R., Jin, Y., Baek, I. J., . . . Nam, S. Y. (2007). Expression pattern of sulfated glycoprotein-2 (SGP-2) mRNA in rat testes exposed to endocrine disruptors. *J Reprod Dev, 53*(5), 1007-1013.

Yoshida, M., Katsuda, S., Tanimoto, T., Asai, S., Nakae, D., Kurokawa, Y., . . . Maekawa, A. (2002). Induction of different types of uterine adenocarcinomas in Donryu rats due to neonatal exposure to high-dose p-t-octylphenol for different periods. *Carcinogenesis, 23*(10), 1745-1750.