# CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

#### SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT OF 1986 (Proposition 65)

#### NOTICE OF ADDITION OF DOCUMENTS AND INFORMATION TO OAL RULEMAKING FILE No. Z-05-0614-06

# AMENDMENT TO TITLE 22, CALIFORNIA CODE OF REGULATIONS, SECTION 12805, SPECIFIC REGULATORY LEVELS: CHEMICALS CAUSING REPRODUCTIVE TOXICITY

# [Proposition 65 Maximum Allowable Dose Level (MADL) for Reproductive Toxicity for Di(2-ethylhexyl)phthalate (DEHP) by Oral Exposure]

#### May 5, 2006

Pursuant to the requirements of Government Code sections 11346.8(d), 11346.9(a)(1), and 11347.1, the Office of Environmental Health Hazard Assessment (OEHHA) is providing notice that documents and other information which the agency has relied upon in proposing amendments to Title 22, California Code of Regulations, section 12805, have been added to the rulemaking file and are available for public inspection and comment.

The purpose of this notice is to enter all relevant documents into the Rulemaking File, OAL File No. Z-05-0614-06. All the documents included in this notice had not been previously included in the Rulemaking File, OAL File No. Z-05-0614-06, but have been considered by OEHHA in establishing the proposed maximum allowable dose levels (MADLs) for DEHP by oral exposure. Of these documents, one is the revised draft OEHHA document supporting the proposed MADLs for DEHP by oral exposure (OEHHA, 2006), two others (Koch et al., 2003 and Stedman's Medical Dictionary, 27<sup>th</sup> edition, 2003) are cited in the revised draft MADL document (OEHHA, 2006) and listed in the References section of this document.

All other documents on the list below have been identified in the Bibliography section of the revised draft OEHHA document supporting proposed MADLs for DEHP by oral exposure (OEHHA, 2006). All the documents identified in the Bibliography section of the document have been considered by OEHHA staff but did not directly contribute to the development of the MADLs and were not cited in the main text in the OEHHA (2006) MADL document. Thus, these papers are sources of potentially relevant information. Some documents identified in this notice are research or review papers that became available to OEHHA after preparation of the draft MADL document was completed and released to the public for comment on June 24, 2005. OEHHA staff reviewed these papers as they became available, and determined that no substantial revision to the MADL document was necessitated by these papers.

These documents are available for inspection at the OEHHA's office located at 1001 "I" Street, 19<sup>th</sup> Floor, Sacramento, CA from **May 5, 2006 through May 22, 2006**, between the hours of 8:00 a.m. and 5:00 p.m. If you have any comments regarding the documents and other information, OEHHA will accept written comments between (date) and (date). All written comments must be submitted to OEHHA by e-mail, mail, fax, courier or hand-delivered, no later than 5:00 p.m. on **May 22, 2006** and addressed to:

Susan Luong Office of Environmental Health Hazard Assessment Street Address: 1001 I Street, 19<sup>th</sup> Floor Sacramento, CA 95814 Mailing Address: P.O. Box 4010 Sacramento, CA 95812 Fax No.: (916) 323-8803 Telephone: (916) 445-6900

Comments transmitted via email should be addressed to: <u>sluong@oehha.ca.gov</u>.

It is requested but not required that written statements or arguments be submitted in triplicate. All written comments received by **May 22, 2006**, which pertain to the abovelisted documents and other information will be reviewed and responded to by OEHHA's staff as part of the compilation of the rulemaking file.

Inquiries concerning the action described in this notice may be directed to Susan Luong, in writing, at the address given above, or by telephone at (916) 445-6900.

## Documents and information added to Notice File No. Z-05-0614-06:

<u>Revised draft OEHHA document supporting proposed MADLs for DEHP by oral</u> <u>exposure:</u>

Office of Environmental Health Hazard Assessment (OEHHA, 2006). Proposition 65 Maximum Allowable Dose Level (MADL) for Reproductive Toxicant for Di(2ethylhexyl)phthalate (DEHP) by Oral Exposure. OEHHA Reproductive and Cancer Hazard Assessment Section, California Environmental Protection Agency, Sacramento, April.

Research papers or document cited and listed as "References" in the OEHHA (2006) document:

Koch HM, Rossbach B, Drexler H, Angerer J (2003). Internal exposure of the general population to DEHP and other phthalates--determination of secondary and primary phthalate monoester metabolites in urine. *Environ Res* **93**, 177-85.

Stedman's Medical Dictionary, 27th edition (2000). Pub. Lippincott Williams & Wilkins. Accessible online at http://www.stedmans.com.

# Research papers or document listed in the Bibliography in the OEHHA (2006) document:

Abbott DH, Hearn JP (1978). Physical, hormonal and behavioural aspects of sexual development in the marmoset monkey, Callithrix jacchus. *J Reprod Fertil* **53**, 155-66.

Agarwal DK, Eustis S, Lamb JC 4th, Jameson CW, Kluwe WM (1986). Influence of dietary zinc on di(2-ethylhexyl)phthalate-induced testicular atrophy and zinc depletion in adult rats. *Toxicol Appl Pharmacol* **84**, 12-24.

Anderson WA, Barnes KA, Castle L, Damant AP, Scotter MJ (2002). Determination of isotopically labelled monoesterphthalates in urine by high performance liquid chromatography-mass spectrometry. *Analyst* **127**, 1193-7.

Arslan M, Weinbauer GF, Schlatt S, Shahab M, Nieschlag E (1993). FSH and testosterone, alone or in combination, initiate testicular growth and increase the number of spermatogonia and Sertoli cells in a juvenile non-human primate (Macaca mulatta). *J Endocrinol* **136**, 235-43.

Asaoka K, Hagihara K, Kabaya H, Sakamoto Y, Katayama H, Yano K (2000). Uptake of phthalate esters, di(n-butyl)phthalate and di(2-ethylhexyl)phthalate, as environmental chemicals in monkeys in Japan. *Bull Environ Contam Toxicol* **64**, 679-85.

Barr AB (1973). Timing of spermatogenesis in four nonhuman primate species. *Fertil Steril* **24**, 381-9.

Behr R, Hunt N, Ivell R, Wessels J, Weinbauer GF (2000). Cloning and expression analysis of testis-specific cyclic 3', 5'-adenosine monophosphate-responsive element modulator activators in the nonhuman primate (Macaca fascicularis): comparison with other primate and rodent species. *Biol Reprod* **62**, 1344-51.

Berensztein EB, Sciara MI, Rivarola MA, Belgorosky A (2002). Apoptosis and proliferation of human testicular somatic and germ cells during prepuberty: high rate of testicular growth in newborns mediated by decreased apoptosis. *J Clin Endocrinol Metab* **87**, 5113-8.

Blair RM, Fang H, Branham WS, Hass BS, Dial SL, Moland CL, Tong W, Shi L, Perkins R, Sheehan DM (2000). The estrogen receptor relative binding affinities of 188 natural and xenochemicals: structural diversity of ligands. *Toxicol Sci* **54**, 138-53.

Borch J, Vinggaard AM, Ladefoged O (2002). The effect of combined prenatal exposure to di(2-ethylhexyl)phthalate and di(2-ethylhexyl)adipate on testosterone production in rats. *Reprod Toxicol* **16(4)**, 406.

Borch J, Vinggaard AM, Ladefoged O (2003). The effect of combined exposure to di(2ethylhexyl)phthalate and diisononylphthalate on testosterone production in rats. *Reprod*  Toxicol 17(4), 487-8.

Brock JW, Caudill SP, Silva MJ, Needham LL, Hilborn ED (2002). Phthalate monoesters levels in the urine of young children. *Bull Environ Contam Toxicol* **68**, 309-14.

Center for the Evaluation of Risks to Human Reproduction (CERHR, 2005). NTP-CERHR Expert Panel Update on the Reproductive and Developmental Toxicity of Di (2ethylhexyl) Phthalate. National Toxicology Program, U.S. Department of Health and Human Services, Research Triangle Park, NC, November.

Chapin RE, Gray TJ, Phelps JL, Dutton SL (1988). The effects of mono-(2-ethylhexyl)phthalate on rat Sertoli cell-enriched primary cultures. *Toxicol Appl Pharmacol* **92**, 467-79.

Chemes HE (2001). Infancy is not a quiescent period of testicular development. *Int J Androl* **24**, 2-7.

Clermont Y (1972). Kinetics of spermatogenesis in mammals: seminiferous epithelium cycle and spermatogonial renewal. *Physiol Rev* **52**, 198-236.

Colon I, Caro D, Bourdony CJ, Rosario O (2000). Identification of phthalate esters in the serum of young Puerto Rican girls with premature breast development. *Environ Health Perspect* **108**, 895-900.

Cortes D, Muller J, Skakkebaek NE (1987). Proliferation of Sertoli cells during development of the human testis assessed by stereological methods. *Int J Androl* **10**, 589-96.

Corton JC, Lapinskas PJ (2005). Peroxisome proliferator-activated receptors: mediators of phthalate ester-induced effects in the male reproductive tract? *Toxicol Sci* **83**, 4-17.

Dalgaard M, Nellemann C, Lam HR, Sorensen IK, Ladefoged O (2001). The acute effects of mono(2-ethylhexyl)phthalate (MEHP) on testes of prepubertal Wistar rats. *Toxicol Lett* **122**, 69-79.

Dalgaard M, Ostergaard G, Lam HR, Hansen EV, Ladefoged O (2000). Toxicity study of di(2-ethylhexyl)phthalate (DEHP) in combination with acetone in rats. *Pharmacol Toxicol* **86**, 92-100.

David RM (2004). Commentary regarding the article by Koch et al.: an estimation of the daily intake of di(2-ethylhexyl)phthalate (DEHP) and other phthalates in the general population. Int. J. Hyg. Environ. Health, 206, 77-83 (2003). *Int J Hyg Environ Health* **207**, 75-6; author reply 77-8.

Dhanya CR, Gayathri NS, Mithra K, Nair KV, Kurup PA (2004). Vitamin E prevents deleterious effects of di (2-ethyl hexyl) phthalate, a plasticizer used in PVC blood storage

bags. Indian J Exp Biol 42, 871-5.

Dhanya CR, Indu AR, Deepadevi KV, Kurup PA (2003). Inhibition of membrane Na(+)-K+ Atpase of the brain, liver and RBC in rats administered di(2-ethyl hexyl) phthalate (DEHP) a plasticizer used in polyvinyl chloride (PVC) blood storage bags. *Indian J Exp Biol* **41**, 814-20.

Eisler JA, Tannenbaum PL, Mann DR, Wallen K (1993). Neonatal testicular suppression with a GnRH agonist in rhesus monkeys: effects on adult endocrine function and behavior. *Horm Behav* **27**, 551-67.

Elcombe CR, Mitchell AM (1986). Peroxisome proliferation due to di(2-ethylhexyl) phthalate (DEHP): species differences and possible mechanisms. *Environ Health Perspect* **70**, 211-9.

Fan LQ, You L, Brown-Borg H, Brown S, Edwards RJ, Corton JC (2004). Regulation of phase I and phase II steroid metabolism enzymes by PPARalpha activators. *Toxicology* **204**, 109-21.

Fisher JS, Millar MR, Majdic G, Saunders PT, Fraser HM, Sharpe RM (1997). Immunolocalisation of oestrogen receptor-alpha within the testis and excurrent ducts of the rat and marmoset monkey from perinatal life to adulthood. *J Endocrinol* **153**, 485-95.

Fisher JS, Turner KJ, Fraser HM, Saunders PT, Brown D, Sharpe RM (1998). Immunoexpression of aquaporin-1 in the efferent ducts of the rat and marmoset monkey during development, its modulation by estrogens, and its possible role in fluid resorption. *Endocrinology* **139**, 3935-45.

Fisher JS (2004). Environmental anti-androgens and male reproductive health: focus on phthalates and testicular dysgenesis syndrome. *Reproduction* **127**, 305-15.

Foster PM (2005). Mode of action: impaired fetal Leydig cell function--effects on male reproductive development produced by certain phthalate esters. *Crit Rev Toxicol* **35**, 713-9.

Foster PM, Mylchreest E, Gaido KW, Sar M (2001). Effects of phthalate esters on the developing reproductive tract of male rats. *Hum Reprod Update* **7**, 231-5.

Fouquet JP, Dang DC (1980). A comparative study of the development of the fetal testis and ovary in the monkey (Macaca fascicularis). *Reprod Nutr Dev* **20**, 1439-59.

Fritz IB (1994). Somatic cell-germ cell relationships in mammalian testes during development and spermatogenesis. *Ciba Found Symp* **182**, 271-4; discussion 274-81.

Fukuwatari T, Suzuki Y, Sugimoto E, Shibata K (2002). Elucidation of the toxic mechanism of the plasticizers, phthalic acid esters, putative endocrine disrupters: effects

of dietary di(2-ethylhexyl)phthalate on the metabolism of tryptophan to niacin in rats. *Biosci Biotechnol Biochem* **66**, 705-10.

Garde SV, Sheth AR, Kulkarni SA (1991a). Cellular distribution of inhibin in marmoset testes during development. *Anat Rec* **229**, 334-8.

Garde SV, Sheth AR, Kulkarni SA (1991b). FSH in testes of marmosets during development: immunocytochemical localization and de novo biosynthesis. *Anat Rec* 231, 119-24.

Giammona CJ, Sawhney P, Chandrasekaran Y, Richburg JH (2002). Death receptor response in rodent testis after mono-(2-ethylhexyl) phthalate exposure. *Toxicol Appl Pharmacol* **185**, 119-27.

Gray LE, Ostby J, Furr J, Wolf CJ, Lambright C, Parks L, Veeramachaneni DN, Wilson V, Price M, Hotchkiss A, Orlando E, Guillette L (2001). Effects of environmental antiandrogens on reproductive development in experimental animals. *Hum Reprod Update* **7**, 248-64.

Green R, Hauser R, Calafat AM, Weuve J, Schettler T, Ringer S, Huttner K, Hu H (2005). Use of di(2-ethylhexyl) phthalate-containing medical products and urinary levels of mono(2-ethylhexyl) phthalate in neonatal intensive care unit infants. *Environ Health Perspect* **113**, 1222-1225.

Gromoll J, Weinbauer GF, Skaletsky H, Schlatt S, Rocchietti-March M, Page DC, Nieschlag E (1999). The Old World monkey DAZ (Deleted in AZoospermia) gene yields insights into the evolution of the DAZ gene cluster on the human Y chromosome. *Hum Mol Genet* **8**, 2017-24.

Gromoll J, Wistuba J, Terwort N, Godmann M, Muller T, Simoni M (2003). A new subclass of the luteinizing hormone/chorionic gonadotropin receptor lacking exon 10 messenger RNA in the New World monkey (Platyrrhini) lineage. *Biol Reprod* **69**, 75-80.

Haider SG, Passia D, Treiber A, Milhorst S (1989). Description of eight phases of spermiogenesis in the marmoset testis. *Acta Anat (Basel)* **135**, 180-4.

Haishima Y, Matsuda R, Hayashi Y, Hasegawa C, Yagami T, Tsuchiya T (2004). Risk assessment of di(2-ethylhexyl)phthalate released from PVC blood circuits during hemodialysis and pump-oxygenation therapy. *Int J Pharm* **274**, 119-29.

Hasmall SC, James NH, Macdonald N, Soames AR, Roberts RA (2000). Species differences in response to diethylhexylphthalate: suppression of apoptosis, induction of DNA synthesis and peroxisome proliferator activated receptor alpha-mediated gene expression. *Arch Toxicol* **74**, 85-91.

Heyn R, Makabe S, Motta PM (1998). Ultrastructural dynamics of human testicular cords

from 6 to 16 weeks of embryonic development. Study by transmission and high resolution scanning electron microscopy. *Ital J Anat Embryol* **103**, 17-29.

Heyn R, Makabe S, Motta PM (2001). Ultrastructural morphodynamics of human Sertoli cells during testicular differentiation. *Ital J Anat Embryol* **106**, 163-71.

Hodges JK, Hearn JP (1977). Effects of immunisation against luteinising hormone releasing hormone on reproduction of the marmoset monkey Callithrixjacchus. *Nature* **265**, 746-8.

Holt WV, Moore HD (1984). Ultrastructural aspects of spermatogenesis in the common marmoset (Callithrix jacchus). *J Anat* **138** ( **Pt 1**), 175-88.

Hoppin JA (2003). Male reproductive effects of phthalates: an emerging picture. *Epidemiology* **14**, 259-60.

Howarth JA, Price SC, Dobrota M, Kentish PA, Hinton RH (2001). Effects on male rats of di-(2-ethylhexyl) phthalate and di-n-hexylphthalate administered alone or in combination. *Toxicol Lett* **121**, 35-43.

Hurst CH, Waxman DJ (2003). Activation of PPARalpha and PPARgamma by environmental phthalate monoesters. *Toxicol Sci* **74**, 297-308.

Husen B, Giebel J, Rune G (1999). Expression of the integrin subunits alpha 5, alpha 6 and beta 1 in the testes of the common marmoset. *Int J Androl* **22**, 374-84.

Jackh R, Rhodes C, Grasso P, Carter JT (1984). Genotoxicity studies on di-(2-ethylhexyl) phthalate and adipate and toxicity studies on di-(2-ethylhexyl) phthalate in the rat and marmoset. *Food Chem Toxicol* **22**, 151-5.

Jackson MR, Edmunds JG (1984). Morphological assessment of testicular maturity in marmosets (Callithrix jacchus). *Lab Anim* **18**, 173-8.

Johnson L, Chaturvedi PK, Williams JD (1992). Missing generations of spermatocytes and spermatids in seminiferous epithelium contribute to low efficiency of spermatogenesis in humans. *Biol Reprod* **47**, 1091-8.

Johnson L, Mckenzie KS, Snell JR (1996). Partial wave in human seminiferous tubules appears to be a random occurrence. *Tissue Cell* **28**, 127-36.

Kang KS, Lee YS, Kim HS, Kim SH (2002). Di-(2-ethylhexyl) phthalate-induced cell proliferation is involved in the inhibition of gap junctional intercellular communication and blockage of apoptosis in mouse Sertoli cells. *J Toxicol Environ Health A* **65**, 447-59.

Kasahara E, Sato EF, Miyoshi M, Konaka R, Hiramoto K, Sasaki J, Tokuda M, Nakano Y, Inoue M (2002). Role of oxidative stress in germ cell apoptosis induced by di(2-

ethylhexyl)phthalate. Biochem J 365, 849-56.

Kavlock R, Boekelheide K, Chapin R, Cunningham M, Faustman E, Foster P, Golub M, Henderson R, Hinberg I, Little R, Seed J, Shea K, Tabacova S, Tyl R, Williams P, Zacharewski T (2002). NTP Center for the Evaluation of Risks to Human Reproduction: phthalates expert panel report on the reproductive and developmental toxicity of di(2ethylhexyl) phthalate. *Reprod Toxicol* **16**, 529-653.

Kelnar CJ, McKinnell C, Walker M, Morris KD, Wallace WH, Saunders PT, Fraser HM, Sharpe RM (2002). Testicular changes during infantile 'quiescence' in the marmoset and their gonadotrophin dependence: a model for investigating susceptibility of the prepubertal human testis to cancer therapy? *Hum Reprod* **17**, 1367-78.

Keys DA, Wallace DG, Kepler TB, Conolly RB (2000). Quantitative evaluation of alternative mechanisms of blood disposition of di(n-butyl) phthalate and mono(n-butyl) phthalate in rats. *Toxicol Sci* **53**, 173-84.

Kholkute SD, Aitken RJ, Lunn SF (1983). Plasma testosterone response to hCG stimulation in the male marmoset monkey (Callithrix jacchus jacchus). *J Reprod Fertil* **67**, 457-63.

Kim HS, Saito K, Ishizuka M, Kazusaka A, Fujita S (2003). Short period exposure to di-(2-ethylhexyl) phthalate regulates testosterone metabolism in testis of prepubertal rats. *Arch Toxicol* **77**, 446-51.

Kluwe WM (1982). Overview of phthalate ester pharmacokinetics in mammalian species. *Environ Health Perspect* **45**, 3-9.

Kubota Y, Nef S, Farmer PJ, Temelcos C, Parada LF, Hutson JM (2001). Leydig insulinlike hormone, gubernacular development and testicular descent. *J Urol* **165**, 1673-5.

Kulkarni SA, Garde SV, Sheth AR (1992). Immunocytochemical localization of bioregulatory peptides in marmoset testes. *Arch Androl* **29**, 87-102.

Kumar RA, Phillips DM (1991). Spermiation and sperm maturation in the marmoset. *Anat Rec* **229**, 315-20.

Kuwada M, Kawashima R, Nakamura K, Kojima H, Hasumi H, Maki J, Sugano S (2002). Neonatal exposure to endocrine disruptors suppresses juvenile testis weight and steroidogenesis but spermatogenesis is considerably restored during puberty. *Biochem Biophys Res Commun* **295**, 193-7.

Lampen A, Zimnik S, Nau H (2003). Teratogenic phthalates and metabolites activate the nuclear receptors PPARs and induce differentiation of F9 cells. *Tox Appl Pharmacol* **188**, 14-23.

Latini G, Gallo F, De Felice C (2004). Birth characteristics and hepatoblastoma risk in young children. *Cancer* **101**, 210.

Lee BC, Pineda JL, Spiliotis BE, Brown TJ, Bercu BB (1983). Male sexual development in the nonhuman primate. III. Sertoli cell culture and age-related differences. *Biol Reprod* **28**, 1207-15.

Li LH, Donald JM, Golub MS (2005). Review on testicular development, structure, function, and regulation in common marmoset. *Birth Defects Res B Dev Reprod Toxicol* **74**, 450-69.

Ljungvall K, Tienpont B, David F, Magnusson U, Torneke K (2004). Kinetics of orally administered di(2-ethylhexyl) phthalate and its metabolite, mono(2-ethylhexyl) phthalate, in male pigs. *Arch Toxicol* **78**, 384-9.

Ljungvall K, Karlsson P, Hulten F, Madej A, Norrgren L, Einarsson S, Rodriguez-Martinez H, Magnusson U (2005). Delayed effects on plasma concentration of testosterone and testicular morphology by intramuscular low-dose di(2ethylhexyl)phthalate or oestradiol benzoate in the prepubertal boar. *Theriogenology* **64**, 1170-84.

Lottrup G, Andersson AM, Leffers H, Mortensen GK, Toppari J, Skakkebaek NE, Main KM (2006). Possible impact of phthalates on infant reproductive health. *Int J Androl* **29**, 172-80.

Lovekamp-Swan T, Davis BJ (2003). Mechanisms of phthalate ester toxicity in the female reproductive system. *Environ Health Perspect* **111**, 139-45.

Lovekamp TN, Davis BJ (2001). Mono-(2-ethylhexyl) phthalate suppresses aromatase transcript levels and estradiol production in cultured rat granulosa cells. *Toxicol Appl Pharmacol* **172**, 217-24.

Lunn SF, Cowen GM, Morris KD, Fraser HM (1992). Influence of the gonad on the degree of suppression induced by an LHRH agonist implant in the marmoset monkey. *J Endocrinol* **132**, 217-24.

Mann DR, Akinbami MA, Gould KG, Paul K, Wallen K (1998). Sexual maturation in male rhesus monkeys: importance of neonatal testosterone exposure and social rank. *J Endocrinol* **156**, 493-501.

Mann DR, Lunn SF, Akinbami MA, Samuel K, Waterfall M, Fraser HM (1999). Effect of neonatal treatment with a GnRH antagonist on development of the cell-mediated immune response in marmosets. *Am J Reprod Immunol* **42**, 175-86.

Manojkumar V, Padmakumaran Nair KG, Santhosh A, Deepadevi KV, Arun P, Lakshmi LR, Kurup PA (1998). Decrease in the concentration of vitamin E in blood and tissues

caused by di(2-ethylhexyl) phthalate, a commonly used plasticizer in blood storage bags and medical tubing. *Vox Sang* **75**, 139-44.

McKee RH (2004). Phthalate exposure and early the larche. *Environ Health Perspect* **112**, A541-3.

McKinnell C, Saunders PT, Fraser HM, Kelnar CJ, Kivlin C, Morris KD, Sharpe RM (2001). Comparison of androgen receptor and oestrogen receptor beta immunoexpression in the testes of the common marmoset (Callithrix jacchus) from birth to adulthood: low androgen receptor immunoexpression in Sertoli cells during the neonatal increase in testosterone concentrations. *Reproduction* **122**, 419-29.

Merkle J, Klimisch HJ, Jackh R (1988). Developmental toxicity in rats after inhalation exposure of di-2-ethylhexylphthalate (DEHP). *Toxicol Lett* **42**, 215-23.

Miraglia T, Telles Filho M, Branco AL (1970). The male reproductive system of the common marmoset (Callithrix jacchus). *Acta Anat (Basel)* **76**, 594-611.

Moore NP (2000). The oestrogenic potential of the phthalate esters. *Reprod Toxicol* **14**, 183-92.

Morrissey RE, Harris MW, Schwetz BA (1989). Developmental toxicity screen: results of rat studies with diethylhexyl phthalate and ethylene glycol monomethyl ether. *Teratog Carcinog Mutagen* **9**, 119-29.

Murature DA, Tang SY, Steinhardt G, Dougherty RC (1987). Phthalate esters and semen quality parameters. *Biomed Environ Mass Spectrom* **14**, 473-7.

Nagano M, McCarrey JR, Brinster RL (2001). Primate spermatogonial stem cells colonize mouse testes. *Biol Reprod* **64**, 1409-16.

Narotsky MG, Hamby BT, Mitchell DS, Weller E, Chinchilli VM, Kavlock RJ (1995). Non-additive developmental toxicity in mixtures of trichloroethylene (TCE), di(2ethylhexyl)phthalate (DEHP), and heptachlor (HEPT). *Fundam Appl Toxicol* **27**, 203-216.

Nunes S, Brown C, French JA (2002). Variation in circulating and excreted estradiol associated with testicular activity in male marmosets. *Am J Primatol* **56**, 27-42.

Ohlson CG, Hardell L (2000). Testicular cancer and occupational exposures with a focus on xenoestrogens in polyvinyl chloride plastics. *Chemosphere* **40**, 1277-82.

Oishi S (1989). Effects of co-administration of di(2-ethylhexyl)phthalate and testosterone on several parameters in the testis and pharmacokinetics of its mono-de-esterified metabolite. *Arch Toxicol* **63**, 289-95.

Oishi S (1990). Effects of phthalic acid esters on testicular mitochondrial functions in the rat. *Arch Toxicol* **64**, 143-7.

Oishi S (1993). Strain differences in susceptibility to di-2-ethylhexyl phthalate-induced testicular atrophy in mice. *Toxicol Lett* **66**, 47-52.

Oishi S, Hiraga K (1980a). Testicular atrophy induced by phthalic acid monoesters: effects of zinc and testosterone concentrations. *Toxicology* **15**, 197-202.

Oishi S, Hiraga K (1980b). Effect of phthalic acid esters on mouse testes. *Toxicol Lett* **5**, 413-6.

Oishi S, Hiraga K (1983). Testicular atrophy induced by di-2-ethylhexyl phthalate: effect of zinc supplement. *Toxicol Appl Pharmacol* **70**, 43-8.

Preslock JP, Steinberger E (1976). Pathway of testosterone biosynthesis in the testis of the marmoset Saguinus oedipus. *Steroids* **28**, 775-84.

Preslock JP, Steinberger E (1977a). Androgen biosynthesis by marmoset testes in vitro. *Gen Comp Endocrinol* **31**, 101-5.

Preslock JP, Steinberger E (1977b). Testicular steroidogenesis in the common marmoset, Callithrix jacchus. *Biol Reprod* **17**, 289-93.

Preslock JP, Steinberger E (1979). Metabolism of pregnenolone and progesterone by testicular microsomes of the baboon Papio anubis and the marmoset Saguinus oedipus. *J Steroid Biochem* **10**, 75-80.

Pretzer D, Ghaida JA, Rune GM (1994). Growth factors (EGF, IGF-I) modulate the morphological differentiation of adult marmoset (Callithrix jacchus) Sertoli cells in vitro. *J Androl* **15**, 398-409.

Prince FP, Mann DR, Fraser HM (1998). Blockade of the hypothalamic-pituitarytesticular axis with a GnRH antagonist in the neonatal marmoset monkey: changes in Leydig cell ultrastructure. *Tissue Cell* **30**, 651-61.

Reddy BS, Rozati R, Reddy S, Kodampur S, Reddy P, Reddy R (2006). High plasma concentrations of polychlorinated biphenyls and phthalate esters in women with endometriosis: a prospective case control study. *Fertil Steril* **85**, 775-9.

Rhodes C, Elcombe CR, Batten PL, Bratt H, Jackson SJ, Pratt IS, Orton TC (1983). The disposition of 14C-di-2-ethylhexylphthalate (DEHP) in the marmoset. *Dev Toxicol Environ Sci* **11**, 579-81.

Richburg JH (2000). The relevance of spontaneous- and chemically-induced alterations in testicular germ cell apoptosis to toxicology. *Toxicol Lett* **112-113**, 79-86.

Richburg JH, Boekelheide K (1996). Mono-(2-ethylhexyl) phthalate rapidly alters both Sertoli cell vimentin filaments and germ cell apoptosis in young rat testes. *Toxicol Appl Pharmacol* **137**, 42-50.

Richburg JH, Johnson KJ, Schoenfeld HA, Meistrich ML, Dix DJ (2002). Defining the cellular and molecular mechanisms of toxicant action in the testis. *Toxicol Lett* **135**, 167-83.

Richburg JH, Nanez A, Gao H (1999). Participation of the Fas-signaling system in the initiation of germ cell apoptosis in young rat testes after exposure to mono-(2-ethylhexyl) phthalate. *Toxicol Appl Pharmacol* **160**, 271-8.

Richburg JH, Nanez A, Williams LR, Embree ME, Boekelheide K (2000). Sensitivity of testicular germ cells to toxicant-induced apoptosis in gld mice that express a nonfunctional form of Fas ligand. *Endocrinology* **141**, 787-93.

Roberts RA, Chevalier S, Hasmall SC, James NH, Cosulich SC, Macdonald N (2002). PPAR alpha and the regulation of cell division and apoptosis. *Toxicology* **181-182**, 167-70.

Rozati R, Reddy PP, Reddanna P, Mujtaba R (2002). Role of environmental estrogens in the deterioration of male factor fertility. *Fertil Steril* **78**, 1187-94.

Rune GM, de Souza P, Merker HJ (1991). Ultrastructural and histochemical characterization of marmoset (Callithrix jacchus) Leydig cells during postnatal development. *Anat Embryol (Berl)* **183**, 179-91.

Schlatt S, Kim SS, Gosden R (2002). Spermatogenesis and steroidogenesis in mouse, hamster and monkey testicular tissue after cryopreservation and heterotopic grafting to castrated hosts. *Reproduction* **124**, 339-46.

Schmezer P, Pool BL, Klein RG, Komitowski D, Schmahl D (1988). Various short-term assays and two long-term studies with the plasticizer di(2-ethylhexyl)phthalate in the Syrian golden hamster. *Carcinogenesis* **9**, 37-43.

Scientific Committee on Toxicity, Ecotoxicity, and the Environment (CSTEE, 2004). Opinion on the results of a second risk assessment of bis(2ethylhexyl) phthalate [DEHP]: human health part. Health and Consumer Protection Directorate-general, European Commission, Brussels.

Sharpe RM (2001). Hormones and testis development and the possible adverse effects of environmental chemicals. *Toxicol Lett* **120**, 221-32.

Sharpe RM (2006). Pathways of endocrine disruption during male sexual differentiation and masculinisation. *Best Pract Res Clin Endocrinol Metab* **20**, 91-110.

Sharpe RM, Martin B, Morris K, Greig I, McKinnell C, McNeilly AS, Walker M (2002). Infant feeding with soy formula milk: effects on the testis and on blood testosterone levels in marmoset monkeys during the period of neonatal testicular activity. *Hum Reprod* **17**, 1692-703.

Sharpe RM, McKinnell C, Kivlin C, Fisher JS (2003). Proliferation and functional maturation of Sertoli cells, and their relevance to disorders of testis function in adulthood. *Reproduction* **125**, 769-84.

Sharpe RM, Fraser HM, Brougham MF, McKinnell C, Morris KD, Kelnar CJ, Wallace WH, Walker M (2003). Role of the neonatal period of pituitary-testicular activity in germ cell proliferation and differentiation in the primate testis. *Hum Reprod* **18**, 2110-7.

Shirota M, Saito Y, Imai K, Horiuchi S, Yoshimura S, Sato M, Nagao T, Ono H, Katoh M (2005). Influence of di-(2-ethylhexyl)phthalate on fetal testicular development by oral administration to pregnant rats. *J Toxicol Sci* **30**, 175-194.

Silva MJ, Barr DB, Reidy JA, Malek NA, Hodge CC, Caudill SP, Brock JW, Needham LL, Calafat AM (2004). Urinary levels of seven phthalate metabolites in the U.S. population from the National Health and Nutrition Examination Survey (NHANES) 1999-2000. *Environ Health Perspect* **112**, 331-8.

Smith D, Trennery P, Farningham D, Klapwijk J (2001). The selection of marmoset monkeys (Callithrix jacchus) in pharmaceutical toxicology. *Lab Anim* **35**, 117-30.

Sonmez M, Turk G, Yuce A. (2005). The effect of ascorbic acid supplementation on sperm quality, lipid peroxidation and testosterone levels of male Wistar rats. *Theriogenology* **63**, 2063-72.

Swan SH (2003). Do environmental agents affect semen quality? *Epidemiology* **14**, 261-2.

Tanaka T (2003). Effects of bis(2-ethylhexyl) phthalate (DEHP) on secondary sex ratio of mice in a cross-mating study. *Food Chem Toxicol* **41**, 1429-32.

Tanaka T (2002). Reproductive and neurobehavioural toxicity study of bis(2-ethylhexyl) phthalate (DEHP) administered to mice in the diet. *Food Chem Toxicol* **40**, 1499-506.

Tickner JA, Schettler T, Guidotti T, McCally M, Rossi M (2001). Health risks posed by use of Di-2-ethylhexyl phthalate (DEHP) in PVC medical devices: a critical review. *Am J Ind Med* **39**, 100-11.

van Wezel AP, van Vlaardingen P, Posthumus R, Crommentuijn GH, Sijm DT (2000). Environmental risk limits for two phthalates, with special emphasis on endocrine disruptive properties. *Ecotoxicol Environ Saf* **46**, 305-21. Veeramachaneni DN (2000). Deteriorating trends in male reproduction: idiopathic or environmental? *Anim Reprod Sci* **60-61**, 121-30.

Waliszewski M, Szymczynski GA (1990). Determination of phthalate esters in human semen. *Andrologia* **22**, 69-73.

Weinbauer GF, Schubert J, Yeung CH, Rosiepen G, Nieschlag E (1998). Gonadotrophinreleasing hormone antagonist arrests premeiotic germ cell proliferation but does not inhibit meiosis in the male monkey: a quantitative analysis using 5-bromodeoxyuridine and dual parameter flow cytometry. *J Endocrinol* **156**, 23-34.

Weinbauer GF, Aslam H, Krishnamurthy H, Brinkworth MH, Einspanier A, Hodges JK (2001). Quantitative analysis of spermatogenesis and apoptosis in the common marmoset (Callithrix jacchus) reveals high rates of spermatogonial turnover and high spermatogenic efficiency. *Biol Reprod* **64**, 120-6.

Wolfe GW, Layton K, Nehrebeckyj L, Wang Y, Chapin R, Rousselle SD, Bishop J (2002). Reproductive effects of diethylhexylphthalate (DEHP) in Sprague-Dawley rats when assessed by the continuous breeding protocol. Toxicologist **66(1-S)**, 234.

Wong JS, Ye X, Muhlenkamp CR, Gill SS (2002). Effect of a peroxisome proliferator on 3 beta-hydroxysteroid dehydrogenase. *Biochem Biophys Res Commun* **293**, 549-53.

Worrell NR, Cook WM, Thompson CA, Gray TJB (1989). Effect of mono-(2ethlyhexyl) phthalate on the metabolism of energy-yielding substrates in rat Sertoli cellenriched cultures. *Toxi in Vitro* **3**, 77-81.