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 RULEMAKING FILE, OAL 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]

August 17, 2005

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 an amendment 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 documents and information added to the rulemaking file are listed below. These documents are available for inspection at the OEHHA's office located at 1001 "I" Street, 19th Floor, Sacramento, CA from **August 17, 2005 through September 1, 2005**, 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 mail, fax, courier or hand-delivered, no later than 5:00 p.m. on <u>September 1, 2005</u>, and addressed to:

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

Comments may also be transmitted via email 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 September 1, 2005, which pertain to the above-listed 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:

Ablake M, Itoh M, Terayama H, Hayashi S, Shoji S, Naito M, Takahashi K, Suna S, Jitsunari F (2004). Di-(2-ethylhexyl) phthalate induces severe aspermatogenesis in mice, however, subsequent antioxidant vitamins supplementation accelerates regeneration of the seminiferous epithelium. *Int J Androl* **27**, 274-81.

Albro PW (1986). Absorption, metabolism, and excretion of di(2-ethylhexyl) phthalate by rats and mice. *Environ Health Perspect* **65**, 293-8.

Albro PW, Chapin RE, Corbett JT, Schroeder J, Phelps JL (1989). Mono-2-ethylhexyl phthalate, a metabolite of di-(2-ethylhexyl) phthalate, causally linked to testicular atrophy in rats. *Toxicol Appl Pharmacol* **100**, 193-200.

Albro PW, Corbett JT, Schroeder JL, Jordan S, Matthews HB (1982a). Pharmacokinetics, interactions with macromolecules and species differences in metabolism of DEHP. *Environ Health Perspect* **45**, 19-25.

Albro PW, Hass JR, Peck CC, Jordan ST, Corbett JT, Schroeder J (1982b). Applications of isotope differentiation for metabolic studies with di-(2-ethylhexyl) phthalate. *J Environ Sci Health B* **17**, 701-14.

Albro PW, Hass JR, Peck CC, Odam DG, Corbett JT, Bailey FJ, Blatt HE, Barrett BB (1981). Identification of the metabolites of di-(2-ethylhexyl) phthalate in urine from the African green monkey. *Drug Metab Dispos* **9**, 223-5.

Albro PW, Lavenhar SR (1989). Metabolism of di(2-ethylhexyl)phthalate. *Drug Metab Rev* **21**, 13-34.

Albro PW, Thomas RO (1973). Enzymatic hydrolysis of di-(2-ethylhexyl) phthalate by lipases. *Biochim Biophys Acta* **306**, 380-90.

Albro PW, Tondeur I, Marbury D, Jordan S, Schroeder J, Corbett JT (1983). Polar metabolites of di-(2-ethylhexyl)phthalate in the rat. *Biochim Biophys Acta* **760**, 283-92.

American Chemistry Council (ACC, 2004). Information pertaining to development of a maximum allowable dose level for di(2-ethylhexyl) phthalate. Submitted to the Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, on May 12, 2004.

Anderson WA, Castle L, Scotter MJ, Massey RC, Springall C (2001). A biomarker approach to measuring human dietary exposure to certain phthalate diesters. *Food Addit Contam* **18**, 1068-74.

Arcadi FA, Costa C, Imperatore C, Marchese A, Rapisarda A, Salemi M, Trimarchi GR, Costa G (1998). Oral toxicity of bis(2-ethylhexyl) phthalate during pregnancy and suckling in the Long-Evans rat. *Food Chem Toxicol* **36**, 963-70.

Aslan AR, Kogan BA, and Gondos B (2003). Testicular development. In: Polin RA, Fox WW, and Abman SH eds. Fetal and Neonatal Physiology. Sunders, Philadelphia, PA. 3rd edi. Volume 2, Chapter 191, pp1950-1960.

Astill BD (1989). Metabolism of DEHP: effects of prefeeding and dose variation, and comparative studies in rodents and the cynomolgus monkey (CMA studies). *Drug Metab Rev* **21**, 35-53.

Awal MA, Kurohmaru M, Ishii M, Andriana BB, Kanai Y, Hayashi Y (2004). Mono-(2ethylhexyl) phthalate (MEHP) induces spermatogenic cell apoptosis in guinea pig testes at prepubertal stage in vitro. *Int J Toxicol* **23**, 349-55.

Banerjee S, Thuillier R, Culty M, Papadopoulos V, Brown TR, Banerjee PP (2002). In utero exposure to di(2-ethylhexyl) phthalate alters growth, tissue organization, and the expression of androgen receptor protein of rat prostate. Biol Reprod **66(Suppl 1)**, 200

Bhattacharya N, Dufour JM, Vo MN, Okita J, Okita R, Kim KH (2005). Differential effects of phthalates on the testis and the liver. *Biol Reprod* **72**, 745-54.

Biegel LB, Hurtt ME, Frame SR, O'Connor JC, Cook JC (2001). Mechanisms of extrahepatic tumor induction by peroxisome proliferators in male CD rats. *Toxicol Sci* **60**, 44-55.

Biegel LB, Liu RC, Hurtt ME, Cook JC (1995). Effects of ammonium perfluorooctanoate on Leydig cell function: in vitro, in vivo, and ex vivo studies. *Toxicol Appl Pharmacol* **134**, 18-25.

Bility MT, Thompson JT, McKee RH, David RM, Butala JH, Vanden Heuvel JP, Peters JM (2004). Activation of mouse and human peroxisome proliferator-activated receptors (PPARs) by phthalate monoesters. *Toxicol Sci* **82**, 170-82.

Boekelheide K, Fleming SL, Johnson KJ, Patel SR, Schoenfeld HA (2000). Role of Sertoli cells in injury-associated testicular germ cell apoptosis. *Proc Soc Exp Biol Med* **225**, 105-15.

Borch J, Ladefoged O, Hass U, Vinggaard AM (2004). Steroidogenesis in fetal male rats is reduced by DEHP and DINP, but endocrine effects of DEHP are not modulated by DEHA in fetal, prepubertal and adult male rats. *Reprod Toxicol* **18**, 53-61.

Borch J, Dalgaard M, Ladefoged O (2005). Early testicular effects in rats perinatally exposed to DEHP in combination with DEHA-apoptosis assessment and

immunohistochemical studies. Reprod Toxicol 19, 517-25.

Chiu SH, Huskey SW (1998). Species differences in N-glucuronidation. *Drug Metab Dispos* **26**, 838-47.

Cho F, Yabe M, Honjo S (1975). The weight of the reproductive organs, hypophysis and thyroid of male cynomolgus monkeys (Macaca fascicularis). *Jikken Dobutsu* **24**, 173-5.

Chu I, Villeneuve DC, Secours V, Franklin C, Rock G, Viau A (1978). Metabolism and tissue distribution of mono-2-ethylhexyl phthalate in the rat. *Drug Metab Dispos* **6**, 146-9.

Collett GP, Betts AM, Johnson MI, Pulimood AB, Cook S, Neal DE, Robson CN (2000). Peroxisome proliferator-activated receptor alpha is an androgen-responsive gene in human prostate and is highly expressed in prostatic adenocarcinoma. *Clin Cancer Res* **6**, 3241-8.

Cook JC, Murray SM, Frame SR, Hurtt ME (1992). Induction of Leydig cell adenomas by ammonium perfluorooctanoate: a possible endocrine-related mechanism. *Toxicol Appl Pharmacol* **113**, 209-17.

Corton JC, Lapinskas PJ (2004). Peroxisome Proliferator-Activated Receptors: Mediators of Phthalate Ester-Induced Effects in the Male Reproductive Tract? *Toxicol Sci.*

Daniel JW, Bratt H (1974). The absorption, metabolism and tissue distribution of di(2-ethylhexyl)phthalate in rats. *Toxicology* **2**, 51-65.

David RM, Moore MR, Finney DC, Guest D (2000b). Chronic toxicity of di(2-ethylhexyl)phthalate in mice. *Toxicol Sci* **58**, 377-85.

Dirven HA, van den Broek PH, Arends AM, Nordkamp HH, de Lepper AJ, Henderson PT, Jongeneelen FJ (1993). Metabolites of the plasticizer di(2-ethylhexyl)phthalate in urine samples of workers in polyvinylchloride processing industries. *Int Arch Occup Environ Health* **64**, 549-54.

Duty SM, Silva MJ, Barr DB, Brock JW, Ryan L, Chen Z, Herrick RF, Christiani DC, Hauser R (2003a). Phthalate exposure and human semen parameters. *Epidemiology* **14**, 269-77.

Duty SM, Singh NP, Silva MJ, Barr DB, Brock JW, Ryan L, Herrick RF, Christiani DC, Hauser R (2003b). The relationship between environmental exposures to phthalates and DNA damage in human sperm using the neutral comet assay. *Environ Health Perspect* **111**, 1164-9.

Duty SM, Calafat AM, Silva MJ, Ryan L, Hauser R (2005). Phthalate exposure and reproductive hormones in adult men. *Hum Reprod* **20**, 604-10.

Elbrecht A, Chen Y, Cullinan CA, Hayes N, Leibowitz M, Moller DE, Berger J (1996). Molecular cloning, expression and characterization of human peroxisome proliferator activated receptors gamma 1 and gamma 2. *Biochem Biophys Res Commun* **224**, 431-7. Festing MF, Altman DG (2002). Guidelines for the design and statistical analysis of experiments using laboratory animals. *ILAR J* **43**, 244-58.

Flurer CI, Zucker H (1987). Difference in serum ascorbate in two species of Callithricidae. *Int J Vitam Nutr Res* **57**, 297-8.

Flurer CI, Zucker H (1989). Ascorbic acid in a New World monkey family: species difference and influence of stressors on ascorbic acid metabolism. *Z Ernahrungswiss* **28**, 49-55.

Fredricsson B, Moller L, Pousette A, Westerholm R (1993). Human sperm motility is affected by plasticizers and diesel particle extracts. *Pharmacol Toxicol* **72**, 128-33.

Gangolli SD (1982). Testicular effects of phthalate esters. *Environ Health Perspect* **45**, 77-84.

Gazouli M, Yao ZX, Boujrad N, Corton JC, Culty M, Papadopoulos V (2002). Effect of peroxisome proliferators on Leydig cell peripheral-type benzodiazepine receptor gene expression, hormone-stimulated cholesterol transport, and steroidogenesis: role of the peroxisome proliferator-activator receptor alpha. *Endocrinology* **143**, 2571-83.

Grasso P, Heindel JJ, Powell CJ, Reichert LE Jr (1993). Effects of mono(2-ethylhexyl) phthalate, a testicular toxicant, on follicle-stimulating hormone binding to membranes from cultured rat Sertoli cells. *Biol Reprod* **48**, 454-9.

Gray LE, Hotchkiss AK, Price M, Wolf CJ, Furr J, Ostby J, Lambright C, Parks L, Wilson V, Bobseine K and others (2001). Adverse effects of antiandrogenic pesticides and toxic substances on reproductive development in the male. Biol Reprod **64**(**Suppl 1**), 87-8

Gray LE Jr, Wolf C, Lambright C, Mann P, Price M, Cooper RL, Ostby J (1999). Administration of potentially antiandrogenic pesticides (procymidone, linuron, iprodione, chlozolinate, p,p'-DDE, and ketoconazole) and toxic substances (dibutyl- and diethylhexyl phthalate, PCB 169, and ethane dimethane sulphonate) during sexual differentiation produces diverse profiles of reproductive malformations in the male rat. *Toxicol Ind Health* **15**, 94-118.

Gray TJ, Beamand JA (1984). Effect of some phthalate esters and other testicular toxins on primary cultures of testicular cells. *Food Chem Toxicol* **22**, 123-31.

Gray TJ, Butterworth KR (1980). Testicular atrophy produced by phthalate esters. *Arch Toxicol Suppl* **4**, 452-5.

Gray TJ, Gangolli SD (1986). Aspects of the testicular toxicity of phthalate esters. *Environ Health Perspect* **65**, 229-35.

Gray TJ, Rowland IR, Foster PM, Gangolli SD (1982). Species differences in the testicular toxicity of phthalate esters. *Toxicol Lett* **11**, 141-7.

Gromoll J, Eiholzer U, Nieschlag E, Simoni M (2000). Male hypogonadism caused by homozygous deletion of exon 10 of the luteinizing hormone (LH) receptor: differential action of human chorionic gonadotropin and LH. *J Clin Endocrinol Metab* **85**, 2281-6.

Hampl JS, Taylor CA, Johnston CS (2004). Vitamin C deficiency and depletion in the United States: the Third National Health and Nutrition Examination Survey, 1988 to 1994. *Am J Public Health* **94**, 870-5.

Hase T, Yoshimura R, Mitsuhashi M, Segawa Y, Kawahito Y, Wada S, Nakatani T, Sano H (2002). Expression of peroxisome proliferator-activated receptors in human testicular cancer and growth inhibition by its agonists. *Urology* **60**, 542-7.

Hauser R, Williams P, Altshul L, Calafat AM (2005). Evidence of interaction between polychlorinated biphenyls and phthalates in relation to human sperm motility. *Environ Health Perspect* **113**, 425-30.

Hilscher B, Engemann A (1992). Histological and morphometric studies on the kinetics of germ cells and immature Sertoli cells during human prespermatogenesis. *Andrologia* **24**, 7-10.

Ishihara M, Itoh M, Miyamoto K, Suna S, Takeuchi Y, Takenaka I, Jitsunari F (2000). Spermatogenic disturbance induced by di-(2-ethylhexyl) phthalate is significantly prevented by treatment with antioxidant vitamins in the rat. *Int J Androl* **23**, 85-94.

Ito Y, Yokota H, Wang R, Yamanoshita O, Ichihara G , Wang H, Kurata Y, Takagi K, Nakajima T (2005). Species differences in the metabolism of di(2-ethylhexyl) phthalate (DEHP) in several organs of mice, rats, and marmosets. *Arch Toxicol* **79**, 147-54.

Ivell R, Bathgate RA (2002). Reproductive biology of the relaxin-like factor (RLF/INSL3). *Biol Reprod* 67, 699-705.

Jarfelt K, Dalgaard M, Hass U, Borch J, Jacobsen H, Ladefoged O (2005). Antiandrogenic effects in male rats perinatally exposed to a mixture of di(2-ethylhexyl) phthalate and di(2-ethylhexyl) adipate. *Reprod Toxicol* **19**, 505-15.

Jones HB, Garside DA, Liu R, Roberts JC (1993). The influence of phthalate esters on Leydig cell structure and function in vitro and in vivo. *Exp Mol Pathol* **58**, 179-93.

Jonsson BA, Richthoff J, Rylander L, Giwercman A, Hagmar L (2005). Urinary phthalate

metabolites and biomarkers of reproductive function in young men. *Epidemiology* **16**, 487-93.

Kennedy GL Jr, Butenhoff JL, Olsen GW, O'Connor JC, Seacat AM, Perkins RG, Biegel LB, Murphy SR, Farrar DG (2004). The toxicology of perfluorooctanoate. *Crit Rev Toxicol* **34**, 351-84.

Kijima K, Toyosawa K, Yasuba M, Matsuoka N, Adachi T, Komiyama M, Mori C (2004). Gene expression analysis of the rat testis after treatment with di(2-ethylhexyl) phthalate using cDNA microarray and real-time RT-PCR. *Toxicol Appl Pharmacol* **200**, 103-10.

Kim HS, Ishizuka M, Kazusaka A, Fujita S (2004). Alterations of activities of cytosolic phospholipase a(2) and arachidonic Acid-metabolizing enzymes in di-(2-ethylhexyl)phthalate-induced testicular atrophy. *J Vet Med Sci* **66**, 1119-24.

Klaunig JE, Babich MA, Baetcke KP, Cook JC, Corton JC, David RM, DeLuca JG, Lai DY, McKee RH, Peters JM, Roberts RA, Fenner-Crisp PA (2003). PPARalpha agonistinduced rodent tumors: modes of action and human relevance. *Crit Rev Toxicol* **33**, 655-780.

Kluin PM, Kramer MF, de Rooij DG (1983). Testicular development in Macaca irus after birth. *Int J Androl* **6**, 25-43.

Koch HM, Preuss R, Drexler H, Angerer J, Bolt HM. Biological monitoring of (DEHP) exposure: the relevance of the oxidative metabolites of Di(2-ethylhexyl)phthalate (DEHP) compared to the classical parameter MEHP. (2004b). Annual Meeting of the International Society of Exposure Analysis, Philadelphia, Pennsylvania, USA, October 17-21, 2004. Abstract M1A-06.

Koch HM, Bolt HM, Preuss R, Angerer J (2005). New metabolites of di(2ethylhexyl)phthalate (DEHP) in human urine and serum after single oral doses of deuterium-labelled DEHP. *Arch Toxicol* (Available online on February. 8, 2005).

Kurata, Y., Makinodan, F., Shimamura, N., Okada, M., and Katoh, M. (2005). Metabolism of di(2-ethylhexyl) phthalate (DEHP) in juvenile and fetal marmoset and rat. *Toxicologist* **84** (S-1), 256.

Lake BG, Brantom PG, Gangolli SD, Butterworth KR, Grasso P (1976). Studies on the effects of orally administered Di-(2-ethylhexyl) phthalate in the ferret. *Toxicology* **6**, 341-56.

Lamb JC 4th, Chapin RE, Teague J, Lawton AD, Reel JR (1987). Reproductive effects of four phthalic acid esters in the mouse. *Toxicol Appl Pharmacol* **88**, 255-69.

Lee J, Park J, Jang B, Knudsen TB (2004). Altered expression of genes related to zinc

homeostasis in early mouse embryos exposed to di-2-ethylhexyl phthalate. *Toxicol Lett* **152**, 1-10.

Lenth RV (2001). Some practical guidelines for effective sample size determination. *Am Statist* **55**, 187-193.

Lhuguenot JC, Mitchell AM, Milner G, Lock EA, Elcombe CR (1985). The metabolism of di(2-ethylhexyl) phthalate (DEHP) and mono-(2-ethylhexyl) phthalate (MEHP) in rats: in vivo and in vitro dose and time dependency of metabolism. *Toxicol Appl Pharmacol* **80**, 11-22.

Li LH, Donald J, Golub M (2004). Testicular development, structure, function, and regulation in common marmosets. Southern California/Northern California Chapters of Society of Toxicology 2004 Annual Meeting, September 30-October 1, 2004, San Diego, CA.

Li H, Kim KH (2003). Effects of mono-(2-ethylhexyl) phthalate on fetal and neonatal rat testis organ cultures. *Biol Reprod* **69**, 1964-72.

Li LH, Jester WF Jr, Orth JM (1998). Effects of relatively low levels of mono-(2-ethylhexyl) phthalate on cocultured Sertoli cells and gonocytes from neonatal rats. *Toxicol Appl Pharmacol* **153**, 258-65.

Liang JH, Sankai T, Yoshida T, Yoshikawa Y (2001). Immunolocalization of proliferating cell nuclear antigen (PCNA) in cynomolgus monkey (Macaca fascicularis) testes during postnatal development. *J Med Primatol* **30**, 107-11.

Liu RC, Hahn C, Hurtt ME (1996a). The direct effect of hepatic peroxisome proliferators on rat Leydig cell function in vitro. *Fundam Appl Toxicol* **30**, 102-8.

Liu RC, Hurtt ME, Cook JC, Biegel LB (1996b). Effect of the peroxisome proliferator, ammonium perfluorooctanoate (C8), on hepatic aromatase activity in adult male Crl:CD BR (CD) rats. *Fundam Appl Toxicol* **30**, 220-8.

Liu K, Lehmann KP, Sar M, Young SS, Gaido KW (2005). Gene expression profiling following in utero exposure to phthalate esters reveals new gene targets in the etiology of testicular dysgenesis. *Biol Reprod* **73**, 180-92.

Maloney EK, Waxman DJ (1999). Trans-activation of PPAR α and PPAR γ by structurally diverse environmental chemicals. *Toxicol Appl Pharmacol* **161**, 209-218.

McKee RH, Butala JH, David RM, Gans G (2004). NTP center for the evaluation of risks to human reproduction reports on phthalates: addressing the data gaps. *Reprod Toxicol* **18**, 1-22.

Modigh CM, Bodin SL, Lillienberg L, Dahlman-Hoglund A, Akesson B, Axelsson G

(2002). Time to pregnancy among partners of men exposed to di(2-ethylhexyl)phthalate. *Scand J Work Environ Health* **28**, 418-28.

Moore RW, Rudy TA, Lin TM, Ko K, Peterson RE (2001). Abnormalities of sexual development in male rats with in utero and lactational exposure to the antiandrogenic plasticizer Di(2-ethylhexyl) phthalate. *Environ Health Perspect* **109**, 229-37.

Muller T, Simoni M, Pekel E, Luetjens CM, Chandolia R, Amato F, Norman RJ, Gromoll J (2004). Chorionic gonadotrophin beta subunit mRNA but not luteinising hormone beta subunit mRNA is expressed in the pituitary of the common marmoset (Callithrix jacchus). *J Mol Endocrinol* **32**, 115-28.

National Center for Health Statistics (2005). Clinical growth charts for infants. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, Hyattsville, MD. Available at http://www.cdc.gov/growthcharts/.

National Institute for Occupational Safety and Health (NIOSH, 1990). *NIOH and NIOSH basis for an Occupational Health Standard: Di (2-ethylhexyl) phthalate (DEHP)*. U.S. Department of Health and Human Services. Public Health Service. Centers for Disease Control. NIOSH.

Nef S, Parada LF (1999). Cryptorchidism in mice mutant for Insl3. Nat Genet 22, 295-9.

Office of Environmental Health Hazard Assessment (OEHHA, 1997). Public Health Goal for Di(2-ethylhexyl) Phthalate (DEHP) in Drinking Water. OEHHA, California Environmental Protection Agency, Sacramento, California, February.

Office of Environmental Health Hazard Assessment (OEHHA, 2000). Air Toxics Hot Spots Program Risk Assessment Guidelines. Part IV. Technical Support Document for Exposure Assessment and Stochastic Analysis. OEHHA, California Environmental Protection Agency, Sacramento, California, September.

Ono H, Saito Y, Imai K, Kato M (2004). Subcellular distribution of di-(2-ethylhexyl)phthalate in rat testis. *J Toxicol Sci* **29**, 113-24.

Orth JM (1982). Proliferation of Sertoli cells in fetal and postnatal rats: a quantitative autoradiographic study. *Anat Rec* **203**, 485-92.

Orth JM, Gunsalus GL, Lamperti AA (1988). Evidence from Sertoli cell-depleted rats indicates that spermatid number in adults depends on numbers of Sertoli cells produced during perinatal development. *Endocrinology* **122**, 787-94.

Park JD, Habeebu SS, Klaassen CD (2002). Testicular toxicity of di-(2-ethylhexyl)phthalate in young Sprague-Dawley rats. *Toxicology* **171**, 105-15.

Payne AH, Hardy MP, and Russell LD (1996). The Leydig Cell. Cache River Press, Clearwater, FL.

Peck CC, Albro PW (1982). Toxic potential of the plasticizer Di(2-ethylhexyl) phthalate in the context of its disposition and metabolism in primates and man. *Environ Health Perspect* **45**, 11-7.

Price CJ, Tyl RW, Marr MC, Myers CB, Sadler BM, Kimmel CA (1988). Reproduction and fertility evaluation of diethylhexy phthalate (CAS No. 117-81-7) in CD-1 mice exposed during gestation. Report No. NTP 88-092.

Rais-Bahrami K, Nunez S, Revenis ME, Short BL, Luban NL (2004). Follow-up study of adolescents exposed to di-2-ethylhexyl phthalate (DEHP) as neonates on extracorporeal membrane oxygenation (ECMO) support. *Environ Health Persp* **112**, 1339-40.

Rhodes C, Orton TC, Pratt IS, Batten PL, Bratt H, Jackson SJ, Elcombe CR (1986). Comparative pharmacokinetics and subacute toxicity of di(2-ethylhexyl) phthalate (DEHP) in rats and marmosets: extrapolation of effects in rodents to man. *Environ Health Perspect* **65**, 299-307.

Rune GM, Pretzer D, De Souza P, Bollmann U, Merker HJ (1992). Ultrastructure of adult and juvenile marmoset (Callithrix jacchus) Sertoli cells in vivo and in vitro. *J Androl* **13**, 560-70.

Russell LD and Griswold MD (1993). The Sertoli Cell. Cache River Press, Clearwater, FL.

Saitoh Y, Usumi K, Nagata T, Marumo H, Imai K, Katoh M (1997). Early changes in the rat testis induced by di-(2-Ethylhexyl) phthalate and 2,5-hexanedione: ultrastructure and lanthanum trace study. *J Toxicol Pathol* 10(1), 51-7

Schilling K, Gembardt C, Hellwig J (1999). Reproduction toxicity of di-2-ethylhexyl phthalate (DEHP). Toxicologist ;48(1-S):147-8

Schmid P, Schlatter C (1985). Excretion and metabolism of di(2-ethylhexyl)phthalate in man. *Xenobiotica* **15**, 251-6.

Schultz R, Yan W, Toppari J, Volkl A, Gustafsson JA, Pelto-Huikko M (1999). Expression of peroxisome proliferator-activated receptor alpha messenger ribonucleic acid and protein in human and rat testis. *Endocrinology* **140**, 2968-75.

Schwetz BA, Rao KS, Park CN (1980). Insensitivity of tests for reproductive problems. *J Environ Pathol Toxicol* **3**, 81-98.

Sharpe RM, Walker M, Millar MR, Atanassova N, Morris K, McKinnell C, Saunders PT,

Fraser HM (2000). Effect of neonatal gonadotropin-releasing hormone antagonist administration on Sertoli cell number and testicular development in the marmoset: comparison with the rat. *Biol Reprod* **62**, 1685-93.

Short RD, Robinson EC, Lington AW, Chin AE (1987). Metabolic and peroxisome proliferation studies with di(2-ethylhexyl)phthalate in rats and monkeys. *Toxicol Ind Health* **3**, 185-95.

Sjoberg P, Bondesson U, Gray TJ, Ploen L (1986). Effects of di-(2-ethylhexyl) phthalate and five of its metabolites on rat testis in vivo and in in vitro. *Acta Pharmacol Toxicol* (*Copenh*) **58**, 225-33.

Sjoberg P, Bondesson U, Kjellen L, Lindquist NG, Montin G, Ploen L (1985). Kinetics of di-(2-ethylhexyl) phthalate in immature and mature rats and effect on testis. *Acta Pharmacol Toxicol (Copenh)* **56**, 30-7.

Smedley JV, Bailey SA, Perry RW, O Rourke CM (2002). Methods for predicting sexual maturity in male cynomolgus macaques on the basis of age, body weight, and histologic evaluation of the testes. *Contemp Top Lab Anim Sci* **41**, 18-20.

Swan SH, Main KM, Liu F, Stewart SL, Kruse RL, Calafat AM, Mao CS, Redmon JB, Ternand CL, Sullivan S, Teague JL, Drobnis EZ, Carter BS, Kelly D, Simmons TM, Wang C, Lumbreras L, Villanueva S, Diaz-Romero M, Lomeli MB, Otero-Salazar E, Hobel C, Brock B, Kwong C, Muehlen A, Sparks A, Wolk A, Whitham J, Hatterman-Zogg M, Maifield M, and The Study for Future Families Research Group (2005). Decrease in anogenital distance among male infants with prenatal phthalate exposure. *Environ Health Perspect* (Available at online May 27, 2005).

Takeuchi S, Iida M, Kobayashi S, Jin K, Matsuda T, Kojima H (2005). Differential effects of phthalate esters on transcriptional activities via human estrogen receptors alpha and beta, and androgen receptor. *Toxicology* **210**, 223-33.

Tanaka T (2005). Reproductive and neurobehavioural effects of bis(2-ethylhexyl) phthalate (DEHP) in a cross-mating toxicity study of mice. *Food Chem Toxicol* **43**, 581-9.

Tanaka A, Adachi T, Takahashi T, Yamaha T (1975). Biochemical studies on phthalic esters I. Elimination, distribution and metabolism of di-(2-ethylhexyl)phthalate in rats. *Toxicology* **4**, 253-64.

Tandon R, Seth PK, Srivastava SP (1991). Effect of in utero exposure to di(2-ethylhexyl)phthalate on rat testes. *Indian J Exp Biol* **29**, 1044-6.

Teerds KJ, de Boer-Brouwer M, Dorrington JH, Balvers M, Ivell R (1999). Identification of markers for precursor and leydig cell differentiation in the adult rat testis following ethane dimethyl sulphonate administration. *Biol Reprod* **60**, 1437-45.

Toda C, Okamoto Y, Ueda K, Hashizume K, Itoh K, Kojima N (2004). Unequivocal estrogen receptor-binding affinity of phthalate esters featured with ring hydroxylation and proper alkyl chain size. *Arch Biochem Biophys* **431**, 16-21.

Tyl RW and Jones-Price C (1984). Teratological evaluation of diethylhexylphthalate (CAS No. 117-81-7) in Fischer 344 rats.: Jefferson, AR, National Center for Toxicological Research.

Tyl RW, Price CJ, Marr MC, Kimmel CA (1988). Developmental toxicity evaluation of dietary di(2-ethylhexyl)phthalate in Fischer 344 rats and CD-1 mice. *Fundam Appl Toxicol* **10**, 395-412.

U.S. Environmental Protection Agency (U.S. EPA, 1996). Guidelines for reproductive toxicity risk assessment. *EPA/630/R-96/009* FRL-5630-6.

U.S. Food and Drug Administration (U.S. FDA, 2001). Safety Assessment of Di (2ethylhexyl)phthalate (DEHP) Released from PVC Medical Devices. Centers for Devices and Rediological Health. U.S. Food and Drug Administration. Rockville, MD.

Voss C, Zerban H, Bannasch P, Berger MR (2005). Lifelong exposure to di-(2-ethylhexyl)-phthalate induces tumors in liver and testes of Sprague-Dawley rats. *Toxicology* **206**, 359-71.

Ward JM, Peters JM, Perella CM, Gonzalez FJ (1998). Receptor and nonreceptormediated organ-specific toxicity of di(2-ethylhexyl)phthalate (DEHP) in peroxisome proliferator-activated receptor alpha-null mice. *Toxicol Pathol* **26**, 240-6.

Williams DT, Blanchfield BJ (1974). Retention, excretion and metabolism of di-(2-ethylhexyl) phthalate administered orally to the rat. *Bull Environ Contam Toxicol* **11**, 371-8.

Wilson VS, Lambright C, Furr J, Ostby J, Wood C, Held G, Gray LE Jr (2004). Phthalate ester-induced gubernacular lesions are associated with reduced insl3 gene expression in the fetal rat testis. *Toxicol Lett* **146**, 207-15.

Wistuba J, Mundry M, Luetjens CM, Schlatt S (2004). Co-grafting of hamster (Phodopus sungorus) and marmoset (Callithrix jacchus) testicular tissues into nude mice does not overcome blockade of early spermatogenic differentiation in primate grafts. *Biol Reprod* **71**, 2087-91.

Zhang FP, Kero J, Huhtaniemi I (1998). The unique exon 10 of the human luteinizing hormone receptor is necessary for expression of the receptor protein at the plasma membrane in the human luteinizing hormone receptor, but deleterious when inserted into the human follicle-stimulating hormone receptor. *Mol Cell Endocrinol* **142**, 165-74.