

10 Literaturverzeichnis

1. Russell WM, Burch RL. The Principles of Humane Experimental Technique. London: Methuen & Co., 1959.
2. Spielmann H. Reproduction and development. *Environ Health Perspect* 1998; 106 Suppl 2:571-576.
3. Klug S, Lewandowski C, Wildi L, Neubert D. Bovine serum: An alternative to rat serum as a culture medium for the rat whole embryo culture. *Toxic in Vitro* 1990; 4 (4/5):598-601.
4. Cockcroft DL. Culture media for postimplantation embryos. *Reprod Toxicol* 1991; 5(3):223-228.
5. Genschow E, Spielmann H, Scholz G, Seiler A, Brown N, Piersma A et al. The ECVAM international validation study on in vitro embryotoxicity tests: results of the definitive phase and evaluation of prediction models. *European Centre for the Validation of Alternative Methods. Altern Lab Anim* 2002; 30(2):151-176.
6. Genschow E, Scholz G, Brown N, Piersma A, Brady M, Clemann N et al. Development of prediction models for three in vitro embryotoxicity tests in an ECVAM validation study. *In Vitro Mol Toxicol* 2000; 13(1):51-66.
7. Piersma AH, Genschow E, Verhoef A, Spanjersberg MQ, Brown NA, Brady M et al. Validation of the postimplantation rat whole-embryo culture test in the international ECVAM validation study on three in vitro embryotoxicity tests. *Altern Lab Anim* 2004; 32(3):275-307.
8. Castell JV, Gomez-Lechon MJ, Ponsoda X, Bort R. In vitro investigation of the molecular mechanisms of hepatotoxicity. *Arch Toxicol Suppl* 1997; 19:313-321.
9. Brantom PG, Bruner LH, Chamberlain m, de Silva O, Dupuis J, Earl LK et al. A summary report of the COLIPA international validation study on alternatives to the draize rabbit eye irritation test. *Toxicology in vitro* 1997; 11(1-2):141-179.
10. Spielmann H. International co-operation: an essential requirement for replacing animal toxicity tests. *Altern Lab Anim* 2001; 29(6):633-648.
11. Spielmann H, Liebsch M. Lessons learned from validation of in vitro toxicity test: from failure to acceptance into regulatory practice. *Toxicol In Vitro* 2001; 15(4-5):585-590.
12. Spielmann H, Liebsch M. Validation successes: chemicals. *Altern Lab Anim* 2002; 30 Suppl 2:33-40.
13. Brown NA, Freeman SJ. Alternative tests for teratogenicity. *Atla* 1984; 12:7-23.
14. Neubert D, Klug S. To which extent and how can animal experiments to replace, supplemented or modified in pharmacological and toxicological research? *Alternatives Research, Proceedings of the 9th Annual Meeting of Japanese Society of Alternatives to Animal Experiments, Kyoto. 1995: 4-8.*

15. Flint OP, Orton TC. An *in vitro* assay for teratogens with cultures of rat embryo mid-brain and limb bud cells. *Toxicol Appl Pharmacol* 1984; 76(2):383-395.
16. Spielmann H, Pohl I, Doering B, Liebsch M, Montanya E. The Embryonic Stem Cell Test, an *In Vitro* Embryotoxicity Test Using Two Permanent Mouse Cell Lines: 3T3 Fibroblasts and Embryonic Stem Cells. *In Vitro Toxicology* 1997; 10(1):119-127.
17. New DAT. Techniques for assessment of teratologic effects: embryo culture. *Environ Health Perspect* 1976; 18:105-110.
18. Eibs HG, Spielmann H, Hagele M. Teratogenic effects of cyproterone acetate and medroxyprogesterone treatment during the pre- and postimplantation period of mouse embryos. I. *Teratology* 1982; 25(1):27-36.
19. Rutledge JC. Developmental toxicity induced during early stages of mammalian embryogenesis. *Mutat Res* 1997; 396(1-2):113-127.
20. New DAT, Coppola PT, Terry S. Culture of explanted rat embryos in rotating tubes. *J Reprod Fert* 1973; 35:135-138.
21. Webster WS, Brown-Woodman PD, Ritchie HE. A review of the contribution of whole embryo culture to the determination of hazard and risk in teratogenicity testing. *Int J Dev Biol* 1997; 41 (2):329-335.
22. Nicholas JS, Rudnick D. The development of rat embryos in tissue cultures. *Proc Nat Acad Sci* 1934; 20(12):656-658.
23. New DAT, Stein KF. Cultivation of post-implantation mouse and rat embryos on plasma clots. *J Embryol exp Morph* 1964; 12 (1):101-111.
24. Nicholas JS. The development of rat embryos in a circulating medium. *Anat Rec* 1938; 70(2):199-210.
25. New DAT. Development of explanted rat embryos in circulating medium. *J Embryol Exp Morph* 1967; 17(3):513-525.
26. New DAT. *Methods in mammalian embryology: Methods for the culture of post-implantation embryos of rodents.* (Daniel JC, ed.) San Francisco: W. H. Freeman & Co., 1971; pp. 305-319.
27. Cockroft DL. A comparative and historical review of culture methods for vertebrates. *Int J Dev Biol* 1997; 41:127-137.
28. New DAT. Technique as the basis of experiment in developmental biology. *Int J Dev Biol* 1997; 41:139-152.
29. van Maele-Fabry G, Picard JJ, Attenon P, Berthet P, Delhaise F, Govers MJ et al. Inter-laboratory evaluation of three culture media for postimplantation rodent embryos. *Reprod Toxicol* 1991; 5(5):417-426.
30. Cockroft DL. Development in culture of rat fetuses explanted at 12.5 and 13.5 days of gestation. *J Embryol Exp Morph* 1973; 29(2):473-483.
31. Fujinaga M, Baden JM. A new method for explanting early postimplantation rat embryos for culture. *Teratology* 1991; 43(1):95-100.

32. New DAT. Whole-embryo culture and the study of mammalian embryos during organogenesis. *Biol Rev* 1978; 53:81-122.
33. Witschi E. Development: Rat: Growth including reproduction and morphological development. (Altman PL and Dittmer DS, eds.) Washington, D.C.: Fed Am Soc Exp Biol 1962; pp. 304-314.
34. O'Rahilly R, Muller F. Developmental stages in human embryos: including a revision of Streeter's "Horizons" and a survey of the Carnegie collection. Washington, DC: Carnegie Institution of Washington. 1987; p. 637.
35. Tabocova S, Hunter ES, Gladen BC. Developmental toxicity of inorganic arsenic in whole embryo: culture oxidation state, dose, time, and gestational age dependence. *Toxicol Appl Pharmacol* 1996; 138(2):298-307.
36. Piersma AH, Attenon P, Bechter R, Govers MJ, Krafft N, Schmid BP et al. Interlaboratory evaluation of embryotoxicity in the postimplantation rat embryo culture. *Reprod Toxicol* 1995; 9(3):275-280.
37. Cockroft DL, New DAT. Abnormalities induced in cultured rat embryos by hyperthermia. *Teratology* 1978; 17(3):277-282.
38. Edwards MJ, Walsh DA, Li Z. Hyperthermia, teratogenesis and the heat shock response in mammalian embryos in culture. *Int J Dev Biol* 1997; 41(2):345-358.
39. Mirkes PE. Effects of acute exposures to elevated temperatures on rat embryo growth and development in vitro. *Teratology* 1985; 32(2):259-266.
40. Smoak IW, Sadler TW. Hypothermia: teratogenic and protective effects on the development of mouse embryos in vitro. *Teratology* 1991; 43(6):635-641.
41. Brown NA, Fabro S. Quantitation of rat embryonic development in vitro: a morphological scoring system. *Teratology* 1981; 24:65-78.
42. van Maele-Fabry G, Delhaise F, Gofflot F, Picard JJ. Developmental table of the early mouse post-implantation embryo. *Toxic in Vitro* 1993; Vol. 7(No.6):719-725.
43. New DAT, Coppola PT. Effects of different oxygen concentrations on the development of rat embryos in culture. *J Reprod Fert* 1970; 21:109-118.
44. Shepard TH, Tanimura T, Park HW. Glucose absorption and utilization by rat embryos. *Int J Dev Biol* 1997; 41(2):307-314.
45. New DAT, Coppola PT, Cockroft DL. Comparison of growth in vitro and in vivo of post-implantation rat embryos. *J Embryol exp Morph* 1976; 36(1):133-144.
46. New DAT, Coppola PT, Cockroft DL. Improved development of head-fold rat embryos in culture resulting from low oxygen and modifications of the culture serum. *J Reprod Fert* 1976; 48:219-222.
47. O'Hara MF, Nibbio BJ, Craig RC, Nemeth KR, Charlap JH, Knudsen TB. Mitochondrial benzodiazepine receptors regulate oxygen homeostasis in the early mouse embryo. *Reprod Toxicol* 2003; 17(4):365-375.

48. Fantel AG, Greenaway JC, Juchau MR. The embryotoxicity of adriamycin in rat embryos in vitro. *Toxicol Appl Pharmacol* 1985; 80(1):155-165.
49. Greenaway JC, Mirkes PE, Walker EA, Juchau MR, Shepard T. The effect of oxygen concentration on the teratogenicity of salicylate, Niridazole, cyclophosphamide, and phosphoramidate mustard in rat embryos in vitro. *Teratology* 1985; 32(2):287-295.
50. Chahoud I, Kwasigroch TE. *Methods in Prenatal Toxicology: Controlled breeding of laboratory animals.* (Neubert D, ed.). Stuttgart, Germany: Georg Thieme Verlag, 1977; pp. 196-200.
51. Fujinaga M, Jackson EC, Baden JM. Interlitter variability and developmental stage of day 11 rat embryos produced by overnight and morning short-period breeding regimens. *Teratology* 1990; 42(5):535-540.
52. Theiler K. *The House Mouse.* New York: Springer-Verlag, 1972.
53. Goedbloed JF, Smits-van Prooijje AE. Quantitative analysis of the temporal pattern of somite formation in the mouse and rat. *Acta Anat* 1986; 125:76-82.
54. Flick B, Klug S. Improvement in standardization of the Whole - Embryo - Culture (WEC): Importance of a more precise staging. *Arch Pharm* 2000; 361(Suppl 4):R 168.
55. Brown NA, Goulding EH, Fabro S. A morphological scoring system for rat embryonic development. *Teratology* 1980; 21:301.
56. van Maele-Fabry G, Delhaise F, Picard JJ. Morphogenesis and quantification of the development of post-implantation mouse embryos. *Toxic in Vitro* 1990; 4(2):149-156.
57. Hansen JM, Contreras KM, Harris C. Methanol, formaldehyde, and sodium formate exposure in rat and mouse conceptuses: a potential role of the visceral yolk sac in embryotoxicity. *Birth Defects Res A Clin Mol Teratol* 2005; 73(2):72-82.
58. Kapron CM, Trasler DG. Genetic determinants of teratogen-induced abnormal development in mouse and rat embryos in vitro. *Int J Dev Biol* 1997; 41(2):337-344.
59. Hansen DK, Grafton TF. Comparison of dexamethasone-induced embryotoxicity in vitro in mouse and rat embryos. *Teratog Carcinog Mutagen* 1994; 14(6):281-289.
60. Andrews JE, Ebron-McCoy M, Logsdon TR, Mole LM, Kavlock RJ, Rogers JM. Developmental toxicity of methanol in whole embryo culture: a comparative study with mouse and rat embryos. *Toxicology* 1993; 81(3):205-215.
61. Hansen DK, Walker RC, Grafton TF. Effect of lithium carbonate on mouse and rat embryos in vitro. *Teratology* 1990; 41(2):155-160.
62. Bechter R. Strain differences in the control incidences of morphological abnormalities in the rat whole embryo culture. *Toxic in Vitro* 1993; 7(3):281-284.
63. Naruse I, Collins M, Scott WJ. Strain differences in the teratogenicity induced by sodium valproate in cultured mouse embryos. *Teratology* 1988; 38(1):87-96.
64. New DAT. Development of rat embryos cultured in blood sera. *J Reprod Fert* 1966; 12:509-524.

65. Steele CE, New DAT. Serum variants causing the formation of double hearts and other abnormalities in explanted rat embryos. *J Embryol Exp Morph* 1974; 31(3):707-719.
66. Nakajima M, Sasaki M, Kobayashi Y, Ohno Y, Usami M. Rat embryo culture using rabbit serum as a medium for developmental toxicity studies. *J Appl Toxicol* 1997; 17(3):185-188.
67. Flynn TJ, Friedman L, Black TN, Klein NW. Methionine and iron as growth factors for rat embryos cultured in canine serum. *The Journal of Experimental Zoology* 1987; 244(2):319-324.
68. Coelho CND, Weber JA, Klein NW, Daniels WG, Hoagland TA. Whole rat embryos require methionine for neural tube closure when cultured on cow serum. *J Nutr* 1989; 119(11):1716-1725.
69. Klein NW, Plenefisch JD, Fredrickson WT, Carey SW, Sackett GP, Burbacher TM et al. Serum from monkeys with histories of fetal wastage causes abnormalities in cultured rat embryos. *Science* 1982; 215(4528):66-69.
70. Steele CE. Human serum as a culture medium for the rat embryo. *Experientia* 1985; 41(12):1601-1603.
71. Chatot CL, Klein NW, Clapper ML, Resor SR, Singer WD, Russman BS et al. Human serum teratogenicity studied by rat embryo culture: Epilepsy, Anticonvulsant drugs, and Nutrition. *Epilep* 1984; 25(2):205-216.
72. Klug S, Lewandowski C, Neubert D. Modification and standardization of the culture of early postimplantation embryos for toxicological studies. *Arch Toxicol* 1985; 58:84-88.
73. Lewandowski C, Klug S, Nau H, Neubert D. Pharmacokinetic aspects of drug effects in vitro: effects of serum protein binding on concentration and teratogenicity of valproic acid and 2-en-valproic acid in whole embryos in culture. *Arch Toxicol* 1986; 58(4):239-242.
74. Klug S, Lewandowski C, Blankenburg G, Merker HJ, Neubert D. Effect of acyclovir on mammalian embryonic development in culture. *Arch Toxicol* 1985; 58(2):89-96.
75. Bechter R, Taccard G. Medium and tissue levels of acyclovir and etretinate in the rat whole embryo culture system. In: Nau H, Scott WJ, Jr., editors. *Pharmacokinetics in Teratogenesis*. 1987: 197-208.
76. Klug S, Lewandowski C, Zappel F, Merker HJ, Nau H, Neubert D. Effects of valproic acid, some of its metabolites and analogues on prenatal development of rats in vitro and comparison with effects in vivo. *Arch Toxicol* 1990; 64(7):545-553.
77. Klug S, Lewandowski C, Merker HJ, Stahlmann R, Wildi L, Neubert D. In vitro and in vivo studies on the prenatal toxicity of five antiviral nucleoside analogues in comparison to aciclovir. *Arch Toxicol* 1991; 65(4):283-291.
78. Seegmiller RE, Harris C, Luchtel DL, Juchau MR. Morphological differences elicited by two weak acids, retinoic and valproic, in rat embryos grown in vitro. *Teratology* 1991; 43(2):133-150.

79. Coelho CN, Klein NW. Methionine and neural tube closure in cultured rat embryos: morphological and biochemical analyses. *Teratology* 1990; 42(4):437-451.
80. Ozolins TR, Oglesby LA, Wiley MJ, Wells PG. In vitro murine embryotoxicity of cyclophosphamide in embryos co-cultured with maternal hepatocytes: development and application of a murine embryo-hepatocyte co-culture model. *Toxicology* 1995; 102(3):259-274.
81. Jayme DW, Epstein DA, Conrad DR. Fetal bovine serum alternatives. *Nature* 1988; 334(6182):547-548.
82. Jochems CE, van der Valk JB, Stafleu FR, Baumans V. The use of fetal bovine serum: ethical or scientific problem? *Altern Lab Anim* 2002; 30(2):219-227.
83. Honn KV, Singley JA, Chavin W. Fetal bovine serum: a multivariate standard. *Proc Soc Exp Biol Med* 1975; 149(2):344-347.
84. Knepper PA, Mayanil CS, Goossens W, McLone DC, Hayes E. The presence of transcription factors in fetal bovine sera. *In Vitro Cell Dev Biol Anim* 1998; 34(2):170-173.
85. Lear D, Clarke CA, Gulamhusein AP, Huxham IM, Beck F. Morphological, total nucleic acid and total protein analyses of rat embryos cultured in supplemented and unsupplemented human serum. *J Anat* 1983; 137(2):279-285.
86. Reti LL, Beck F, Bulman S. Culture of 9 1/2-day rat embryos in human serum supplemented and unsupplemented with rat serum. *J Exp Zool* 1982; 223:197-199.
87. Priscott PK. Rat post-implantation embryo culture using heterologous serum. *Aust J Exp Biol Med Sci* 1983; 61(Pt 1):47-55.
88. Usami M, Nakaura S, Kawashima K, Tanaka S, Takanaka A. Culture of postimplantation rat embryos in rabbit serum for the identification of the growth factor in fractionated rat serum. *J Exp Zool* 1992; 264:214-218.
89. Gunberg DL. In vitro development of postimplantation rat embryos cultured in dialyzed rat serum. *Teratology* 1976; 14(1):65-70.
90. Usami M, Ohno Y. Partial purification and characterization of serum embryotrophic factor required for early postimplantation growth of rat embryos in culture. *J Exp Zool* 1996; 276 (6):403-414.
91. Ulger H, Pratten MK. The in vitro effects of low molecular weight serum fractions on embryonic Wistar rat (*Rattus norvegicus*) development. *Anat Histol Embryol* 1999; 28(4):265-269.
92. Gray CW, Morgan PM, Kane MT. Purification of an embryotrophic factor from commercial bovine serum albumin and its identification as citrate. *J Reprod Fert* 1992; 94:471-480.
93. Gulamhusein AP, Pratten MK, Williams CA, Beck F. The effect of macromolecular rat serum fractions on conceptuses cultured in human serum: role of transferrin. *J Anat* 1990; 168:113-121.

94. Katoh M, Kimura R, Shoji R. Embryogenesis-promoting factors in rat serum. *J Exp Zool* 1998; 281(3):188-200.
95. Klein NW, Minghetti PP, Jackson SK, Vogler MA. Serum protein depletion by cultured rat embryos (1). *J Exp Zool* 1978; 203(2):313-318.
96. Priscott PK, Gough PG, Barnes RD. Serum protein depletion by cultured post-implantation rat embryos. *Experientia* 1983; 39(9):1042-1043.
97. Pratten MK, Brooke AM, Broome SC, Beck F. The effect of epidermal growth factor, insulin and transferrin on the growth-promoting properties of serum depleted by repeated culture of postimplantation rat embryos. *Development* 1988; 104(1):137-145.
98. Cockroft DL. Nutrient requirements of rat embryos undergoing organogenesis in vitro. *J Reprod Fert* 1979; 57:505-510.
99. Cockroft DL. Changes with gestational age in the nutritional requirements of postimplantation rat embryos in culture. *Teratology* 1988; 38:281-290.
100. Ulger H, Karabulut AK, Pratten MK. The growth promoting effects of bFGF, PD-ECGF and VEGF on cultured postimplantation rat embryos deprived of serum fractions. *J Anat* 2000; 197(Pt 2):207-219.
101. Pratten MK. The role of exogenous growth-promoting factors and their receptors in embryogenesis. *Reprod Toxicol* 1998; 12(2):201-207.
102. Tebbs CA, Cumberland PF, Pratten MK. The role of maternally derived epidermal growth factor and the epidermal growth factor receptor during organogenesis in the rat embryo. *J Anat* 1997; 190(Pt 4):491-503.
103. Chatot CL, Klein NW, Piatete J, Pierro C. Successful culture of rat embryos on human serum: Use in the detection of teratogens. *Science* 1980; 207:1471-1473.
104. Huxham IM, Beck F. Maternal transferrin uptake by and transfer across the visceral yolk sac of the early postimplantation rat conceptus in vitro. *Dev Biol* 1985; 110(1):75-83.
105. Moore-Scott BA, Gordon J, Blackburn CC, Condie BG, Manley NR. New serum-free in vitro culture technique for midgestation mouse embryos. *Genesis* 2003; 35(3):164-168.
106. Clarkson SG, Doering JV, Runner MN. Growth of postimplantation mouse embryos cultured in a serum-supplemented chemically defined medium. *Teratology* 1969; 2(3):181-185.
107. Schmid BP, Trippmacher A, Bianchi A. Validation of the whole embryo culture method for in vitro teratogenicity testing. *Dev Toxicol Environ Sci* 1983; 11:563-566.
108. Brown NA. Teratogenicity testing in vitro: status of validation studies. *Arch Toxicol Suppl* 1987; 11:105-114.
109. Cicurel L, Schmid BP. Post-implantation embryo culture: validation with selected compounds for teratogenicity testing. *Xenobiotica* 1988; 18(6):617-624.

110. Klug S, Creech KJ, Wildi E, Merker HJ, Persaud TV, Nau H et al. Influence of 13-cis and all-trans retinoic acid on rat embryonic development in vitro: correlation with isomerisation and drug transfer to the embryo. *Arch Toxicol* 1989; 63(3):185-192.
111. Klug S, Thiel R, Schwabe R, Merker HJ, Neubert D. Toxicity of beta-blockers in a rat embryo culture: concentration-response relationships and tissue concentration. *Arch Toxicology* 1994; 68:375-384.
112. Piersma AH, Bechter R, Krafft N, Schmid BP, Stadler J, Verhoef A et al. An interlaboratory evaluation of five pairs of teratogens and non-teratogens and non teratogens in post-implantation rat embryo culture. *Atla* 1996; 24(2):201-209.
113. Spielmann H, Liebsch M, Reinhardt C. [ERGATT/ECVAM Workshop on Acceptance of Validated Alternative Methods: Amden III]. *ALTEX* 1998; 15(1):18-22.
114. Balls M., Blaauboer BJ, Brusik D, Frazier J, Lamb D, Pemberton M et al. Report and recommendation of the CAAT/ERGATT workshop on the validation of toxicity test procedures. *Atla* 1990; 18:313-337.
115. Balls M, Blaauboer BJ, Fentem JH, Bruner L, Combes RD, Ekwall B et al. Practical Aspects of the Validation of Toxicity Test Procedures. *Atla* 1995; 23:129-147.
116. Curren RD, Southee JA, Spielmann H, Liebsch M, Fentem JH, Balls M. The Role of Prevalidation in the Development, Validation and Acceptance of Alternative Methods. *Atla* 1995; 23:211-217.
117. OECD. Final Report of the OECD Workshop on Harmonization of Validation and Acceptance Criteria for Alternative Toxicological Test Methods. Paris, France: OECD. 60pp. 1996.
118. NIEHS. Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the Ad Hoc Interagency Coordinating Committee on the Validation of Alternative Methods. Research Triangle Park, NC, USA: NIEHS. 105pp. 1997.
119. Finnell RH. Teratology: general considerations and principles. *J Allergy Clin Immunol* 1999; 103(2 Pt 2):S337-S342.
120. Shepard TH. Catalog of Teratogenic Agents. Sixth edition. Baltimore and London: The John Hopkins University Press, 1989.
121. Smith MK, Kimmel GL, Kochhar DM, Shepard TH, Spielberg SP, Wilson JG. A selection of candidate compounds for in vitro teratogenesis test validation. *Teratog Carcinog Mutagen* 1983; 3(6):461-480.
122. Brown NA. Selection of test chemicals for the ECVAM international validation study on in vitro embryotoxicity tests. European Centre for the Validation of Alternative Methods. *Altern Lab Anim* 2002; 30(2):177-198.
123. Flick B, Klug S. Whole embryo culture: an important tool in developmental toxicology today. *Curr Pharm Des* 2006; 12(12):1467-1488.
124. Amacher DE, Stadler J, Schomaker SJ, Verseil C. The Comparative Testing of Eight Coded Chemicals in the Rat Limb Bud Micromass and Rat Embryo Culture Systems. *Atla* 1996; 24:945-952.

125. Bennett GD, Wlodarczyk B, Calvin JA, Craig JC, Finnell RH. Valproic acid-induced alterations in growth and neurotrophic factor gene expression in murine embryos [corrected]. *Reprod Toxicol* 2000; 14(1):1-11.
126. Andrews JE, Ebron-McCoy MT, Bojic U, Nau H, Kavlock RJ. Stereoselective dysmorphogenicity of the enantiomers of the valproic acid analogue 2-N-propyl-4-pentynoic acid (4-yn-VPA): cross-species evaluation in whole embryo culture. *Teratology* 1997; 55(5):314-318.
127. Dunty WC, Jr., Chen SY, Zucker RM, Dehart DB, Sulik KK. Selective vulnerability of embryonic cell populations to ethanol-induced apoptosis: implications for alcohol-related birth defects and neurodevelopmental disorder. *Alcohol Clin Exp Res* 2001; 25(10):1523-1535.
128. van Maele-Fabry G, Gofflot F, Clotman F, Picard JJ. Alterations of mouse embryonic branchial nerves and ganglia induced by ethanol. *Neurotoxicol Teratol* 1995; 17(4):497-506.
129. Giavini E, Broccia L, Prati M, Bellomo D, Menegola E. Effects of ethanol and acetaldehyde on rat embryos developing in vitro. *In vitro Cell Dev Biol* 1992; 28A:205-210.
130. Lee YM, Osumi-Yamashita N, Ninomiya Y, Moon CK, Eriksson U, Eto K. Retinoic acid stage-dependently alters the migration pattern and identity of hindbrain neural crest cells. *Development* 1995; 121(3):825-837.
131. Watanabe T, Pratt RM. Effects of retinoic acid on embryonic development of mice in culture. *Experientia* 1991; 47(5):493-497.
132. Klug S, Lewandowski C, Wildi L, Neubert D. All-trans retinoic acid and 13-cis-retinoic acid in the rat whole-embryo culture: abnormal development due to the all-trans isomer. *Arch Toxicol* 1989; 63(6):440-444.
133. Grafton TF, Bazare JJJ, Hansen DK, Sheehan DM. The in vitro embryotoxicity of 5-Fluorouracil in rat embryos. *Teratology* 1987; 36(3):371-377.
134. Kuwagata M, Takashima H, Nagao T. A comparison of the in vivo and in vitro response of rat embryos to 5-fluorouracil. *J Vet Med Sci* 1998; 60(1):93-99.
135. Tierschutzbericht 2005. <http://www.bmelv.de/>. 2006.
136. Rusche B. The 3Rs and animal welfare - conflict or the way forward? *ALTEX* 2003; 20(Suppl 1):63-76.
137. Locker A. [Animal testing ethics and human testing. Thoughts on our conduct with and our relationship to animals]. *ALTEX* 2004; 21(4):221-226.
138. Piersma AH. Validation of alternative methods for developmental toxicity testing. *Toxicol Lett* 2004; 149(1-3):147-153.
139. Homepage European Commission. http://europa.eu.int/comm/index_en.htm . 2006.
140. Chemikaliengesetz vom 16.09.1980. <http://www.bmu.de/chemikalien/doc/2672.php> . 2004.

141. Commission of the European Communities. White Paper - Strategy for a future Chemicals Policy. http://europa.eu/eur-lex/en/com/wpr/2001/com2001_0088en01.pdf . 2006.
142. Anon. Report of the 2355th Session of the Council "Environment". The Council of the European Union . 7-6-2001. http://ue.eu.int/ueDocx/cms_Data/docs/pressdata/en/envir/09116-Communique-1.doc.html. 2004.
143. Fujinaga M, Brown NA, Baden JM. Comparison of staging systems for the gastrulation and early neurulation period in rodents: a proposed new system. *Teratology* 1992; 46(2):183-190.
144. Ryan L. The use of generalized estimating equations for risk assessment in developmental toxicity. *Risk Anal* 1992; 12(3):439-447.
145. Fujinaga M, Hoffman BB, Baden JM. Axial rotation in rat embryos: morphological analysis and microsurgical study on the role of the allantois. *Teratology* 1995; 51(2):94-106.
146. Lowry DH, Farr NJ, Rosenbrough AL, Randall R. Protein measurement with the Folin phenol reagent. *J Biol Chem* 1951; 193:265-275.
147. Sanyal MK, Wiebke EA. Oxygen requirement for in vitro growth and differentiation of the rat conceptus during organogenesis phase of embryo development. *Biol Reprod* 1979; 20:639-647.
148. Calvert NI, Pratten MK, Beck F. Trophic factors in rat serum and embryonic development. *Biochem Soc Trans* 1986; 14:980-981.
149. Brown NA, Clarke DO, McCarthy A. Adaptation of postimplantation embryos to culture: membrane lipid synthesis and response to valproate. *Reprod Toxicol* 1991; 5(3):245-253.
150. Gofflot F, van Maele-Fabry G, Picard JJ. Mouse whole embryo culture in serum diluted with Waymouth medium: A study of valproic acid teratogenicity. *Atla* 1995; 23:677-687.
151. Menegola E, Broccia ML, Prati M, Giavini E. Morphological alterations induced by sodium valproate on somites and spinal nerves in rat embryos. *Teratology* 1999; 59(2):110-119.
152. Ritchie HE, Brown-Woodman PD, Korabelnikoff A. Effect of co-administration of retinoids on rat embryo development in vitro. *Birth Defects Res A Clin Mol Teratol* 2003; 67(6):444-451.
153. Coberly S, Lammer E, Alashari M. Retinoic acid embryopathy: case report and review of literature. *Pediatr Pathol Lab Med* 1996; 16(5):823-836.
154. Sulik KK, Dehart DB, Rogers JM, Chernoff N. Teratogenicity of low doses of all-trans retinoic acid in presomite mouse embryos. *Teratology* 1995; 51(6):398-403.
155. Gressens P, Gofflot F, Maele-Fabry G, Misson JP, Gadisseux JF, Evrard P et al. Early neurogenesis and teratogenesis in whole mouse embryo cultures. Histochemical, immunocytological and ultrastructural study of the premigratory neuronal-glial units in nor-

- mal mouse embryo and in mouse embryos influenced by cocaine and retinoic acid. *J Neuropathol Exp Neurol* 1992; 51(2):206-219.
156. Wilkemeyer MF, Chen SY, Menkari CE, Brenneman DE, Sulik KK, Charness ME. Differential effects of ethanol antagonism and neuroprotection in peptide fragment NAP-VSIPQ prevention of ethanol-induced developmental toxicity. *Proc Natl Acad Sci U S A* 2003; 100(14):8543-8548.
 157. Gressens P, Lammens M, Picard JJ, Evrard P. Ethanol-induced disturbances of gliogenesis and neuronogenesis in the developing murine brain: an in vitro and in vivo immunohistochemical and ultrastructural study. *Alcohol Alcohol* 1992; 27(3):219-226.
 158. Clode AM, Pratten MK, Beck F. The effect of ethanol on the growth of rat embryos: The role of stage dependency and hyperosmolality. *Arch Toxicol Suppl* 1987; 11:163-167.
 159. Brown NA, Goulding EH, Fabro S. Ethanol embryotoxicity: direct effects on mammalian embryos in vitro. *Science* 1979; 206(4418):573-575.
 160. Anwar M, Beck F. Evaluation of human serum as a culture medium for studies of rat embryonic development in vitro. *Reprod Toxicol* 1988; 2:135-140.
 161. Beck F, Huxham IM, Gulamhusein AP. Growth of rat embryos in the serum of alcohol drinkers. *Ciba Found Symp* 1984;(105):218-233.
 162. Sadler TW, Phillips LS, Balkan W, Goldstein S. Somatomedin inhibitors from diabetic rat serum alter growth and development of mouse embryos in culture. *Diabetes* 1986; 35(8):861-865.
 163. Balkan W, Rooman RP, Hurst-Evans A, Phillips LS, Goldstein S. Somatomedin inhibitors from human serum produce abnormalities in mouse embryos in culture. *Teratology* 1988; 38(1):79-86.
 164. Steele CE, Plenefisch JD, Klein NW. Abnormal development of cultured rat embryos in rat and human sera prepared after vitamin A ingestion. *Experientia* 1982; 38(10):1237-1239.
 165. Chatot CL, Klein NW. Reversal of teratogenic activity in human serum from anticonvulsant treated epileptics using vitamin and amino acid supplements. *Teratology* 1982;33A.
 166. Cockroft DL. Vitamin deficiency and neural tube defects: human and animal studies. *Hum Reprod* 1991; 6(1):148-157.
 167. Gupta M, Beck F. Growth of 9.5-day rat embryos in human serum. *J Embryol exp Morph* 1983; 76:1-8.
 168. Cumberland PF, Pratten MK. Differences in binding characteristics of rat and human transferrin by rat visceral yolk sac placenta. *Placenta* 1993; 14(3):287-307.
 169. New DAT. The culture of vertebrate embryos. London: Logos Press, 1966.
 170. Hodgson J. To treat or not to treat: that is the question for serum. *Biotechnology (N Y)* 1995; 13(4):333-343.
 171. Bohn B. Fatal bovine serum? *Biotechnology (N Y)* 1995; 13(9):926-927.

172. Harris MJ, Juriloff DM. Mini-review: toward understanding mechanisms of genetic neural tube defects in mice. *Teratology* 1999; 60(5):292-305.
173. Cockroft DL, Coppola PT. Teratogenic effects of excess glucose on head-fold rat embryos in culture. *Teratology* 1977; 16(2):141-146.
174. Freeman SJ, Coakley ME, Brown NA. Post-implantation embryo culture for studies of teratogenesis. In: Dress RL, editor. *A practical approach. Biochemical Toxicology*, 1987: 83-109.
175. Jojovic M, Wolf F, Mangold U. Epidermal growth factor, vascular endothelial growth factor and progesterone promote placental development in rat whole-embryo culture. *Anat Embryol (Berl)* 1998; 198(2):133-139.
176. Scholz G, Pohl I, I, Seiler A, Bremer S, Brown NA, Piersma AH et al. Results of the first phase of the ECVAM project "prevalidation and validation of three in vitro embryotoxicity tests". *ALTEX* 1998; 15(1):3-8.
177. Klug S. Whole embryo culture: Interpretation of abnormal development in vitro. *Reprod Toxicol* 1991; 5(3):237-244.
178. Kao J, Brown NA, Schmid B, Goulding EH, Fabro S. Teratogenicity of valproic acid: in vivo and in vitro investigations. *Teratog Carcinog Mutagen* 1981; 1:367-382.
179. Chakraborty I, Das SK, Dey SK. Differential expression of vascular endothelial growth factor and its receptor mRNAs in the mouse uterus around the time of implantation. *J Endocrinol* 1995; 147(2):339-352.
180. Karabulut AK, Layfield R, Pratten MK. Growth-promoting effects of different fractions of extra-embryonic coelomic fluid on embryonic development. *Anat Histol Embryol* 2000; 29(4):225-234.
181. Yi XJ, Jiang HY, Lee KK, WS O, Tang PL, Chow PH. Expression of vascular endothelial growth factor (VEGF) and its receptors during embryonic implantation in the golden hamster (*Mesocricetus auratus*). *Cell Tissue Res* 1999; 296(2):339-349.
182. Karabulut AK, Layfield R, Pratten MK. Growth promoting effects of human placental lactogen during early organogenesis: a link to insulin-like growth factors. *J Anat* 2001; 198(Pt 6):651-662.
183. Pratten MK. The role of exogenous growth-promoting factors and their receptors in organogenesis. *Int J Dev Biol* 1997; 41(2):319-328.
184. Daughaday WH, Rotwein P. Insulin-like growth factors I and II. Peptide, messenger ribonucleic acid and gene structures, serum, and tissue concentrations. *Endocr Rev* 1989; 10(1):68-91.
185. Korgun ET, Dohr G, Desoye G, Demir R, Kayisli UA, Hahn T. Expression of insulin, insulin-like growth factor I and glucocorticoid receptor in rat uterus and embryo during decidualization, implantation and organogenesis. *Reproduction* 2003; 125(1):75-84.
186. Nakago S, Funakoshi T, Ueda Y, Maruo T. Regulation of circulating levels of IGF-I in pregnant rats: changes in nitrogen balance correspond with changes in serum IGF-I concentrations. *J Endocrinol* 1999; 163(2):373-377.

187. Travers JP, Exell L, Huang B, Town E, Lammiman MJ. Insulin and insulinlike growth factors in embryonic development. *Diabetes* 1992; 41(3):318-324.
188. Hwa V, Oh Y, Rosenfeld RG. The insulin-like growth factor-binding protein (IGFBP) superfamily. *Endocr Rev* 1999; 20(6):761-787.
189. Baserga R, Rubin R. Cell cycle and growth control. *Crit Rev Eukaryot Gene Expr* 1993; 3(1):47-61.
190. Paria BC, Das SK, Andrews GK, Dey SK. Expression of the epidermal growth factor receptor gene is regulated in mouse blastocysts during delayed implantation. *Proc Natl Acad Sci U S A* 1993; 90(1):55-59.
191. Hortsch M, Schlessinger J, Gootwine E, Webb CG. Appearance of functional EGF receptor kinase during rodent embryogenesis. *EMBO J* 1983; 2(11):1937-1941.
192. Popliker M, Shatz A, Avivi A, Ullrich A, Schlessinger J, Webb CG. Onset of endogenous synthesis of epidermal growth factor in neonatal mice. *Dev Biol* 1987; 119(1):38-44.
193. Ferrara N, Davis-Smyth T. The biology of vascular endothelial growth factor. *Endocr Rev* 1997; 18(1):4-25.
194. Gerber HP, Dixit V, Ferrara N. Vascular endothelial growth factor induces expression of the antiapoptotic proteins Bcl-2 and A1 in vascular endothelial cells. *J Biol Chem* 1998; 273(21):13313-13316.
195. Bates DO, Curry FE. Vascular endothelial growth factor increases hydraulic conductivity of isolated perfused microvessels. *Am J Physiol* 1996; 271(6 Pt 2):H2520-H2528.
196. Jakeman LB, Armanini M, Phillips HS, Ferrara N. Developmental expression of binding sites and messenger ribonucleic acid for vascular endothelial growth factor suggests a role for this protein in vasculogenesis and angiogenesis. *Endocrinology* 1993; 133(2):848-859.
197. Ferrara N. Role of vascular endothelial growth factor in regulation of physiological angiogenesis. *Am J Physiol Cell Physiol* 2001; 280(6):C1358-C1366.
198. Matsuzawa T, Nomura M, Unno T. Clinical pathology reference ranges of laboratory animals. Working Group II, Nonclinical Safety Evaluation Subcommittee of the Japan Pharmaceutical Manufacturers Association. *J Vet Med Sci* 1993; 55(3):351-362.
199. Redl H, Bahrami S, Schlag G, Traber DL. Clinical detection of LPS and animal models of endotoxemia. *Immunobiology* 1993; 187(3-5):330-345.
200. Deb K, Chaturvedi MM, Jaiswal YK. Gram-negative bacterial endotoxin-induced infertility: a birds eye view. *Gynecol Obstet Invest* 2004; 57(4):224-232.
201. Dubin NH, Bornstein DR, Gong Y. Use of endotoxin as a positive (toxic) control in the mouse embryo assay. *J Assist Reprod Genet* 1995; 12(2):147-152.
202. Leazer TM, Barbee B, Ebron-McCoy M, Henry-Sam GA, Rogers JM. Role of the maternal acute phase response and tumor necrosis factor alpha in the developmental toxicity of lipopolysaccharide in the CD-1 mouse(1). *Reprod Toxicol* 2002; 16(2):173-179.

203. Leazer TM, Barbee B, Ebron-McCoy M, Henry-Sam GA, Rogers JM. Role of the maternal acute phase response and tumor necrosis factor alpha in the developmental toxicity of lipopolysaccharide in the CD-1 mouse. *Reprod Toxicol* 2002; 16(2):173-179.
204. Lichanska AM, Hume DA. Origins and functions of phagocytes in the embryo. *Exp Hematol* 2000; 28(6):601-611.
205. Brown NA, Spielmann H, Wiger R. Screening Chemicals for Reproductive Toxicity: The Current Alternatives. *Atla* 1994; 23:868-882.
206. Wilson JG, Jordan RL, Schumacher H. Potentiation of the teratogenic effects of 5-fluorouracil by natural pyrimidines. I. Biological aspects. *Teratology* 1969; 2(2):91-97.
207. Skalko RG, Jacobs DM. The effect of 5-fluorouracil on [3H]nucleoside incorporation into the DNA of mouse embryos and maternal tissues. *Exp Mol Pathol* 1978; 29(3):303-315.
208. Shah RM, MacKay RA. Teratological evaluation of 5-fluorouracil and 5-bromo-2-deoxyuridine on hamster fetuses. *J Embryol Exp Morphol* 1978; 43:47-54.:47-54.
209. Wilson JG. Use of rhesus monkeys in teratological studies. *Fed Proc* 1971; 30(1):104-109.
210. Shuey DL, Setzer RW, Lau C, Zucker RM, Elstein KH, Narotsky MG et al. Biological modeling of 5-fluorouracil developmental toxicity. *Toxicology* 1995; 102(1-2):207-213.
211. Giavini E, Menegola E, Niederreither K, Vermot J, Schuhbauer B, Chambon P et al. Gene-teratogen interactions in chemically induced congenital malformations. *Biol Neonate* 2004; 85(2):73-81.
212. Nau H, Rating D, Koch S, Hauser I, Helge H. Valproic acid and its metabolites: placental transfer, neonatal pharmacokinetics, transfer via mother's milk and clinical status in neonates of epileptic mothers. *J Pharmacol Exp Ther* 1981; 219(3):768-777.
213. De Luca LM. Retinoids and their receptors in differentiation, embryogenesis, and neoplasia. *FASEB J* 1991; 5(14):2924-2933.
214. Robertson J, Polifka JE, Avner M, Chambers C, Delevan G, Koren G et al. A survey of pregnant women using isotretinoin. *Birth Defects Res A Clin Mol Teratol* 2005; 73(11):881-887.
215. Nau H. Teratogenicity of isotretinoin revisited: species variation and the role of all-trans-retinoic acid. *J Am Acad Dermatol* 2001; 45(5):S183-S187.
216. Goodlett CR, Horn KH, Zhou FC. Alcohol teratogenesis: mechanisms of damage and strategies for intervention. *Exp Biol Med (Maywood)* 2005; 230(6):394-406.
217. Clode AM, Pratten MK, Beck F. A stage-dependent effect of ethanol on 9.5-day rat embryos grown in culture and the role played by the concomitant rise in osmolality. *Teratology* 1987; 35:395-403.
218. Wynter JM, Walsh DA, Webster WS, Mcewen SE, Lipson AH. Teratogenesis after acute alcohol exposure in cultured rat embryos. *Teratog Carcinog Mutagen* 1983; 3(5):421-428.

219. Priscott PK. The effects of ethanol on rat embryos developing in vitro. *Biochem Pharmacol* 1982; 31(22):3641-3643.
220. Campbell MA, Fantel AG. Teratogenicity of acetaldehyde in vitro: relevance to the fetal alcohol syndrome. *Life Science* 1983; 32(23):2641-2647.
221. Sulik KK, Johnston MC, Webb MA. Fetal alcohol syndrome: embryogenesis in a mouse model. *Science* 1981; 214(4523):936-938.
222. van Maele-Fabry G, Clotman F, Gofflot F, Bosschaert J, Picard JJ. Postimplantation mouse embryos cultured in vitro. Assessment with whole-mount immunostaining and in situ hybridization. *Int J Dev Biol* 1997; 41 (2):365-374.
223. Gofflot F, Maele-Fabry G, Picard JJ. Cranial nerves and ganglia are altered after in vitro treatment of mouse embryos with valproic acid (VPA) and 4-en-VPA. *Brain Res Dev Brain Res* 1996; 93(1-2):62-69.
224. van Maele-Fabry G, Gofflot F, Picard JJ. Defects in the development of branchial nerves and ganglia induced by in vitro exposure of mouse embryos to mercuric chloride. *Teratology* 1996; 53(1):10-20.
225. Flick B, Klug S. *In vitro* toxicity of N-methyl-pyrrolidone and its three metabolites using the whole embryo culture test (WEC) including more precise endpoints. 5. World Congress of Alternative Methods in Life Sciences 2005, Berlin.
226. Flick B, Klug S. *In vitro* toxicity of N-methyl-pyrrolidone (NMP) in comparison to ethanol using the whole embryo culture test (WEC) with consideration of new endpoints. *Naunyn-Schmiedeberg's Archives of Pharmacology* 2006; 372(Suppl 1), 100.