

Jorma Toppari

Report on my sabbatical year in the Department of Growth and Reproduction, Copenhagen, Denmark

I'm very grateful for the grant of the Sabbatical Leave Programme from the European Society for Paediatric Endocrinology through an educational grant from Lilly USA, LLC. This made it possible for me to work in the Department of Growth and Reproduction, Copenhagen, Denmark, from August 1, 2010 to July 31, 2011. I had close collaboration with the large group of scientists and clinical endocrinologists, including Anders Juul, Niels E. Skakkebaek, Katharina M. Main, Niels Jorgensen and many younger colleagues.

We focussed our work on the on-going puberty follow-up study where we studied the developmental (fetal and early childhood) effects on pubertal maturation. The ultimate end of pubertal maturation is adult reproductive capacity, and this was the other focus area. We analyzed results of the 15-year-follow up studies of semen quality in young adults. To assess the influence of environment on development we analyzed both chemical exposures and gene-environment interactions in children and young men with or without reproductive disorders, such as cryptorchidism, hypospadias, hypospermatogenesis, and/or testicular cancer. The year gave also a possibility to write some reviews on these topics, including an invited WHO monograph on possible developmental effects of endocrine disrupters on child health (Toppari et al., 2011).

This year's work will be published over the next few years, but already this year we achieved interesting results that were published, e.g.:

Semen quality of Finnish men has deteriorated during the last 15 years, and at the same time the incidence of testicular cancer has rapidly increased in Finland (Jorgensen et al., 2011). Thus, Finnish men appear to suffer from the same reproductive health problems that raised concern in other European countries earlier.

Smoking was recognized as a risk factor for poor spermatogenesis, not only after fetal exposure, but also in adults (Ravnborg et al., 2011).

Mild analgesic drugs, such as paracetamol, was found to affect reproductive development in rats and to be associated to a slightly increased risk of cryptorchidism in Danish children (Kristensen et al., 2011). However, the causal relationship remains open.

On behalf of ESPE and American Pediatric Endocrine Society we wrote a Call for Action Statement The Exposure of Fetuses and Children to Endocrine Disrupting Chemicals, that was published in Journal of Clinical Endocrinology and Metabolism (Skakkebaek et al., 2011).

I attach here a list of publications from 2010 (many of which certainly stem from previous research) and 2011.

Once again, I want to extend my gratitude to ESPE for this great opportunity.

Sincerely,

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Publications 2010 – Aug 2011

I have bolded the articles that were co-authored with the colleagues from the Danish host lab.

- 1. Salonen J, Rajpert-De Meyts E, Mannisto S, Nielsen JE, Graem N, Toppari J, Heikinheimo M: Differential developmental expression of transcription factors GATA-4 and GATA-6, their cofactor FOG-2 and downstream target genes in testicular carcinoma in situ and germ cell tumors. Eur J Endocrinol. 62(3):625-631, 2010.**
2. Sironen A, Hansen J, Thomsen B, Andersson M, Vilkki J, Toppari J and Kotaja N: Expression of SPEF2 During Mouse Spermatogenesis and Identification of IFT20 as an Interacting Protein. Biol Reprod. 82(3):580-90, 2010.
3. Nurmio M, Tena-Sempere M, Toppari J.: Orexins and the Regulation of the Hypothalamic-Pituitary-Testicular Axis. Acta Physiol (Oxf). 198:349-54, 2010. Review
- 4. Krysiak-Baltyn K, Toppari J, Skakkebaek NE, Jensen TS, Virtanen HE, Schramm KW, Shen H, Vartiainen T, Kiviranta H, Taboureau O, Brunak S and Main KM.: Country-specific chemical signatures of persistent environmental compounds in breast milk. Int J Androl. 33:270-8, 2010**
- 5. Jørgensen N, Liu F, Andersson AM, Vierula M, Irvine DS, Auger J, Brazil CK, Drobnis EZ, Jensen TK, Jouannet P, Overstreet JW, Redmon JB, Sparks A, Toppari J, Wang C, Skakkebaek NE, Swan SH: Serum inhibin-b in fertile men is strongly correlated with low but not high sperm counts: a coordinated study of 1,797 European and US men. Fertil Steril. 94:2128-34, 2010.**
- 6. Main KM, Skakkebaek NE, Virtanen HE, Toppari J. Genital anomalies in boys and the environment. Best Pract Res Clin Endocrinol Metab. 24:279-89, 2010. Review**
7. Meikar O, Da Ros M, Liljebäck H, Toppari J and Kotaja N: Accumulation of piRNAs in the chromatoid bodies purified by a novel isolation protocol. Exp Cell Res. 316:1567-75, 2010.
- 8. Toppari J and Juul A: Trends in puberty onset in humans and environmental modifiers. Mol Cell Endocr. 324(1-2):39-44, 2010. Review**
9. Bois C, Delalande C, Nurmio M, Parvinen M, Zanatta L, Toppari J, Carreau S. Age- and cell-related gene expression of aromatase and estrogen receptors in the rat testis. J Mol Endocrinol. 45:147-59, 2010.
- 10. Toppari J, Virtanen HE, Main KM, Skakkebaek NE. Cryptorchidism and hypospadias as a sign of testicular dysgenesis syndrome (TDS): Environmental connection. Birth Defects Res A Clin Mol Teratol. 88:910-9, 2010. Review**
- 11. Andersson AM, Bay K, Grigor KM, Toppari J, Skakkebaek NE. Proceedings of the 5th Copenhagen Workshop on endocrine disruptors: ubiquitous endocrine disruptors and possible human health effects. Preface. Int J Androl. 33:251, 2010.**
- 12. Olea N, Sharpe R, Jegou B, Toppari J, Skakkebaek NE, Schlatt S, Heindel J (2010) Male reproductive health. Science Policy Briefing 40, European Science Foundation, September 2010, WWW.esf.org**
- 13. Toppari J, Virtanen HE and Skakkebaek NE: Environmental contaminants and reproductive and fertility effects in the male: Possible role of fetal exposure. In: Environmental Impacts on Reproductive Health and Fertility. Ed. by TJ Woodruff, SJ Janssen, LJ Guillette and LC Giudice. Cambridge University Press, Cambridge, UK. pp. 147-153, 2010.**
14. Bonde J-P and Toppari J: Prevention of male infertility: environmental and systematic diseases on male fertility. In: Andrology. EAU/ESAU Course Guidelines. Ed. by L Björndahl, A Giwercman, H Tournaye and W Weidner. Informa Health Care, New York, N.Y., USA. pp. 164-175, 2010.

15. **Rajpert-De Meyts E, Main KM, Toppari J and Skakkebaek NE: Testicular dysgenesis syndrome, cryptorchidism, hypospadias, and testicular tumors. In: Endocrinology, Adult and Pediatric, 6th ed. Ed. by JL Jameson and LJ De Groot. Saunders-Elseviers, Philadelphia, PA, USA. pp. 2499-2513, 2010.**
16. **Kristensen DM, Hass U, Lesné L, Lottrup G, Jacobsen PR, Desdoits-Lethimonier C, Boberg J, Petersen JH, Toppari J, Jensen TK, Brunak S, Skakkebaek NE, Nellemann C, Main KM, Jégou B and Leffers H: Intrauterine exposure to mild analgesics is a risk factor for development of male reproductive disorders in human and rat. *Hum Reprod* 26:235-44, 2011.**
17. McCarver G, Bhatia J, Chambers C, Clarke R, Etzel R, Foster W, Hoyer P, Leeder JS, Peters J, Rissman E, Rybak M, Sherman C, Toppari J, and Turner K NTP-CERHR Expert Panel Report on the Developmental Toxicity of Soy Infant Formula. *Birth Defects Research* (in press) Review
18. **Jørgensen N, Vierula M, Jacobsen R, Pukkala E, Perheentupa A, Virtanen HE, Skakkebaek NE and Toppari J: Recent adverse trends in semen quality and testis cancer incidence of Finnish men. *Int J Androl* 34(4 Pt 2):e37-48, 2011.**
19. **Fernandez MF, Duran I, Olea N, Avivar C, Vierula M, Toppari J, Skakkebaek NE and Jørgensen N: Semen quality and reproductive hormone levels in men from Southern Spain. *Int J Androl* 2011 Feb 18. doi: 10.1111/j.1365-2605.2010.01131.x. [Epub ahead of print]**
20. Kyrönlähti A, Euler R, Bielinska M, Schoeller EL, Moley KH, Toppari J, Heikinheimo M, Wilson DB. GATA4 regulates Sertoli cell function and fertility in adult male mice. *Mol Cell Endocrinol* 333:85-95, 2011.
21. **Bay K, Main KM, Toppari J, Skakkebaek NE; Medscape. Testicular descent: INSL3, testosterone, genes and the intrauterine milieu. *Nat Rev Urol* 8:187-96, 2011. Review**
22. Nurmio M, Joki H, Kallio J, Määttä JA, Väänänen HK, Toppari J, Jahnukainen K, Laitala-Leinonen T. Receptor tyrosine kinase inhibition causes simultaneous bone loss and excess bone formation within growing bone in rats. *Toxicol Appl Pharmacol* 254(3):267-79, 2011.
23. Hou M, Stukenborg JB, Nurmio M, Andersson M, Toppari J, Söder O, Jahnukainen K. Ontogenesis of ap-2 γ expression in rat testes. *Sex Dev* 5:188-96, 2011.
24. **Ravnborg TL, Jensen TK, Andersson AM, Toppari J, Skakkebaek NE, Jørgensen N. Prenatal and adult exposures to smoking are associated with adverse effects on reproductive hormones, semen quality, final height and body mass index. *Hum Reprod* 26:1000-11, 2011.**
25. Laitinen EM, Tommiska J, Virtanen HE, Oehlandt H, Koivu R, Vaaralahti K, Toppari J, Raivio T. Isolated cryptorchidism: No evidence for involvement of genes underlying isolated hypogonadotropic hypogonadism. *Mol Cell Endocrinol* 341:35-8, 2011.
26. Korhonen HM, Meikar O, Prakash Yadav R, Papaioannou MD, Yannick Romero Y, Da Ros M, Herrera PL, Toppari J, Nef S, and Kotaja N: Dicer is required for haploid male germ cell differentiation in mice. *PLoS ONE*, 2011 (accepted).
27. Karlberg S, Toppari J, Karlberg N, Nurmio M, Karikoski R, Jalanko H and Lipsanen-Nyman M: Testicular failure and male infertility in the monogenic mulibrey nanism disorder. *J Clin Endocr Metab*, 2011 (in press).
28. **Rajpert-De Meyts E, Toppari J. European Academy of Andrology revives the International Journal of Andrology Award and Lecture. *Int J Androl* 34:1, 2011.**
29. Huhtaniemi I, Toppari J. Male reproductive endocrinology. Preface. *Best Pract Res Clin Endocrinol Metab* 25(2):vii, 2011.
30. **Skakkebaek NE, Andersson AM, Juul A, Jensen TK, Almstrup K, Toppari J, Jørgensen N. Commentary: sperm counts, data responsibility, and good scientific practice. *Epidemiology* 22:620-1, 2011.**

- 31. Skakkebaek NE, Toppari J, Söder O, Gordon CM, Dival S, Draznin M. The Exposure of Fetuses and Children to Endocrine Disrupting Chemicals: A European Society for Paediatric Endocrinology (ESPE) and Pediatric Endocrine Society (PES) Call to Action Statement. J Clin Endocrinol Metab. 2011 Aug 10. Epub**
- 32. Toppari J and Skakkebaek NE: Adverse trends in male reproductive health in twp Nordic countries indicate environmental problems. In: Multis-System Endocrine Disruption. Ed. by J-P Bourguignon, B Jégou, B Kerdelhue, J Toppari and Y Christen. Research and Perspectives in Endocrine Interactions. Springer-Verlag, Berlin, Germany, 2011. (in press)**
- 33. Toppari, J., Boas, M., Virtanen, H.E., Adamsson, A., Main, K.M., Juul, A., and Skakkebaek, N.E. (2011). Possible developmental early effects of endocrine disrupters on child health. WHO (in press)**