Estrogenic Activity and Reproductive Organ Toxicity of Alkylphenols

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Abstract

Recent reports on estrogenic activity and reproductive organ toxicity of alkylphenols were reviewed, citing 32 references, and the risk on human health was discussed. Alkylphenols detected environmentally are from alkylphenol-polyethoxylates, and consist of approx. 80% para-nonylphenol and 20% para-octylphenol. Although para-nonylphenols is a mixture of various branched para-nonylphenols and para-octylphenol is almost entirely para-tertiary octylphenol, nonylphenol and octylphenol instead of the accurate structural names are used in this article.

Estrogenic Activity

Nonylphenol induced growth of MCF-7 cells and transcriptional activity in estrogen receptor gene- and reporter gene-transfected MCF-7 cells and yeasts but only to the extent of one over 1,000 to 300,000 that of 17β-estradiol. Octylphenol also induced both growth and transcriptional activity, being approximately 10 to 30 fold more potent than nonylphenol. Nonylphenol showed uterotrophic activity such as an increase of uterus weight in immature and ovariectomised female rats, from as a dose as 40 mg/kg/day on 3 days oral administration. This uterotrophic activity was completely inhibited by ICl 182,780, a typical estrogen receptor antagonist. Octylphenol also showed uterotrophic
activity in immature rats at 166 mg/kg/day after 3-days s.c. injections and in ovariectomised rats at 25 mg/kg/day with 14-days s.c. injections.

**Effects on female reproductive organs**

Nonylphenol given to female rats at 250 mg/kg/day by gavage for 28 days exerted no significant effects on any additional reproductive parameters with the OECD test guideline 407. Octylphenol at 100 mg/kg/day administered by s.c. injections to female rats from postnatal day 1-15 (every other day) induced earlier vaginal opening, persistent estrus after maturation and increased proliferation in the endometrial epithelium. Octylphenol at 100 mg/kg/day given by s.c. injection to adult female rats for 28 days induced increase of uterine weight and increased proliferation in the endometrial epithelium.

**Effects on mammary glands**

Nonylphenol at 0.073 mg/kg/day by implanted mini-pump for 11 days induced cell proliferation and differentiation in the mammary glands of immature female Noble rats. However, those effects were not confirmed even at a dose of 53.2 mg/kg/day by the same procedure in two additional studies using Noble and Alpk:AP rats. Nonylphenol at 100 mg/kg/day by gavage for 11 days induced only weak cell proliferation in the mammary glands of female Alpk:AP rats.

**Effects on male reproductive organs**

Histopathological changes in vas deferens and reduction of sperm counts and weights of testis and epididymis were observed in adult male rats on oral administration of nonylphenol at more than 100 mg/kg/day. The same effects in offspring male rats were shown by oral administration of nonylphenol to pregnant rats from gestation day 7 to lactation week 3 and to the offspring until week 10. A no adverse effect level (NOAEL) to male reproductive toxicity by oral administration could not be established. Furthermore, reduction of testis and accessory organ weights was observed on i.p. injections of more than 0.8 mg/kg/day to male rats on postnatal days 1 to 15. In the same system, 8.0 mg/kg/day induced cryptorchidism and lowered fertility. However, no significant effects on male reproductive organs were observed by s.c..
administration of octylphenol even at a dose of 200 mg/kg/day to postnatal male rats.

**Toxicokinetics**

A study of octylphenol in rats indicated that the bioavailability by gavage ranged from 2 to 12% and the blood concentration profile after a single administration was the same as that with 14 days consecutive administration. On the other hand, there was no detection of octylphenol in blood and tissues of rats after 28 days administration in drinking water at the maximum soluble concentration. Toxicokinetics study on volunteer using $^{13}$C-nonylphenol showed a high rate of conjugation and a quick disappearance from the blood with a 2-3 hour half-life. In the general population, measured values of nonylphenol and octylphenol in adipose tissue have been found to be under the detection limit. It was shown by *in vitro* experiment that both nonylphenol and octylphenol are very quickly conjugated with glucuronic acid and sulfuric acid, or otherwise metabolized.

**Detailed analysis of endocrine organs in various toxicity studies**

A feeding study of nonylphenol for 90 days indicated no significant effects on reproductive functions of male and female rats including sperm counts, mobility, estrous and cycles. The NOAEL was established as 50 mg/kg/day, because slight decrease of body weights and increase of renal weights were observed at higher doses. Reproductive toxicity of nonylphenol in a rat multigeneration feeding study was observed by low sperm counts, prolongation of the estrous cycle and lowered uterus weights. As some changes were also observed at 50 mg/kg/day, the NOAEL for reproductive toxicity was considered to be 15 mg/kg/day.

**Risk assessment**

It was estimated that the estrogenic equivalence of the highest intake of nonylphenol was 1/100 of daidzein, a natural phytoestrogen. A second estimation reported a safety margin of about 20,000, comparing the highest intake of nonylphenol and a NOAEL of 50 mg/kg/day (90 days study), and a safety margin of about 3,000, comparing the blood levels of nonylphenol (at highest intake) and 17β-
estradiol, and the relative estrogenic activity of nonylphenol. Both reports concluded the low concern of human risk of nonylphenol at present.

**Conclusion**

Human risk from alkylphenols by oral intake is considered to be low at present, based on the relative estrogenic activity of nonylphenol and/or octylphenol, the accumulated data of effects on mammary gland and male reproductive organs, detailed analyses of repeated dose and multigeneration studies, and toxicokinetic data including that from a human study.