Endocrine disrupting chemicals: Effects on mammary gland development and female genital malformations

BACKGROUND: Endocrine disrupting chemicals (EDCs) may contribute to reproductive changes in boys in the Western world, however, less is known about influence of EDCs in women. The incidence of precocious breast development is increasing in USA and Europe and mammary gland development has been suggested as particularly sensitive to endocrine disruption. Mammary gland examination in toxicological studies may be useful for improving knowledge on possible influences of EDCs on human mammary glands and also be useful for detection of endocrine disrupting effects of chemicals as part of safety testing. To improve knowledge on possible influences of endocrine disrupters on female reproductive system, the effects of EDCs on genital malformations in females and the development of mammary glands were studied in the present project.

AIMS: The aims for the studies on male and female mammary gland development and female genital malformations were (i) to investigate the effects of EDCs with estrogenic or anti-androgenic mode of action, (ii) to develop methods for evaluation of the effects of EDCs in offspring exposed during foetal and postnatal development until weaning and (iii) to investigate the sensitivity of these methods by examining the effects of perinatal exposure to different environmentally relevant EDCs in offspring.

METHODS: Rat studies were used as a model for humans. Rat dams were exposed to EDCs during pregnancy and the lactation period. Female and male offspring were examined for changes in mammary gland development before puberty in whole mounted mammary glands and in adults in histological sections of the mammary glands. Moreover, female offspring were evaluated for external genital malformations. The EDCs studied for mammary gland effects were the estrogenic compounds ethinyl estradiol and genistein, a mixture of phytoestrogens, and a mixture of environmentally relevant estrogenic EDCs of various origins. Moreover, mixtures of antiandrogenic chemicals were investigated. These include a mixture of pesticides and a mixture of environmentally relevant anti-androgenic EDCs of various origins. Finally, a mixture with environmentally relevant EDCs with dissimilar modes of action was studied. Female genital malformations were investigated for the compounds ethinyl estradiol, bisphenol A and epoxiconazole as well as the mixtures of environmentally relevant EDCs.

RESULTS: Mammary glands in rats were sensitive to EDCs. EDCs with estrogenic mode of action appeared to increase mammary outgrowth in prepubertal female rats and a potent model compound, ethinyl estradiol, increased the density in females and males and the number of terminal end buds in male rats. Histological examination showed changes in epithelial morphology in male (hypertrophic epithelium) and female (lobuloalveolar morphology) mammary glands in adult rats exposed to phytoestrogens. Anti-androgenic chemicals showed signs of feminisation of adult male mammary glands. No effects of anti-androgens were observed in female mammary glands. The histological changes observed in adult female and male mammary glands were not present consistently in the groups of estrogenic or anti-androgenic chemicals and may be due to other modes of action of the chemicals. Female genital malformations were affected by the potent estrogenic chemical ethinyl estradiol, only.

In studies on exposure to anti-androgens, other endpoints, such as nipple retention showed effects in male rats at dose levels where no effects were observed in male or female mammary glands or female external genitals. However, in studies on estrogenic chemicals, marked effects on prepubertal female rat mammary glands were observed at lower levels than those affecting other endpoints studied.

CONCLUSION: The present findings in rats suggest that EDCs may affect mammary gland development in women and men, although risk assessment including comparison with exposure is necessary to draw conclusion on this. Histological examination of mammary glands are included in the extended one-generation OECD guideline studies, however, risk assessment of estrogenic chemicals may overlook the effects on mammary glands if outgrowth in females PD22 is not investigated. Further studies are necessary to confirm the high sensitivity of the distance to the lymph node in female mammary gland whole mounts and to validate this endpoint.

General information
Publication status: Published
Organisations: National Food Institute, Division of Toxicology and Risk Assessment
Contributors: Mandrup, K.
Number of pages: 240
Publication date: 2013

Publication information
Place of publication: Kgs. Lyngby
Publisher: Technical University of Denmark (DTU)
ISBN (Print): 978-87-92763-76-1
Original language: English
Electronic versions:
Karen_Mandrup_afhandling..PDF