Estetrol (E4) is a natural estrogen produced by the human fetal liver during pregnancy. By contrast to other estrogens, E4 does not elicit harmful effects on liver and vascular functions. Due to these unique properties, E4 seems to be safer and suitable for gynaecological applications such as for contraception or hormone replacement therapy. However, the impact of E4 on breast remains to be clearly defined. In that view, this study evaluates the effect of E4 used alone or in association with estradiol (E2) on human breast epithelial (HBE) cells proliferation and on mouse mammary gland growth. Human breast samples were obtained from women undergoing mammoplasty reduction. HBE cells were exposed in vitro to increasing doses of E2 and/or E4. Moreover, prepubertal ovariectomized mice were treated orally with E2 and/or E4 for 14 days. The effects of these estrogenic treatments on mammary gland growth were then evaluated and quantified using a new unique computerized method.

Compared to E2, we observed that E4 acts as a weak estrogen in both models. Indeed, E4 stimulates the proliferation of HBE cells and promotes the growth of the murine mammary gland in a lower extent than E2. This stimulatory effect of E4 can be prevented by anti-estrogens ICI 182780, a pure estrogen receptor alpha (ERα) antagonist and by tamoxifen, suggesting that ERα mediates the estrogenic effect of E4 in the breast. Interestingly, when E4 is administered concomitantly to E2, it significantly antagonizes the strong stimulatory effect of E2 in both human breast cells in vitro and in murine mammary glands in vivo.

Altogether, our data characterized E4 as a weak estrogen that could antagonized the proliferative effect of E2 on breast. These data strongly validate E4 as a high potential candidate for clinical use that exhibits a safer profile than E2, including a reduced impact on breast proliferation.