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# Pharmacokinetic interactions of selective serotonin reuptake inhibitors

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## Abstract
Endocrine disrupting chemicals represent a group of environmental pollutants interfering with synthesis, metabolism and binding of natural hormones. They are widely used in the production of industrial, pharmaceuticals and personal care products and due to their high bioconcentration and low biodegradation rates, humans are constantly exposed to them. Increasing body of literature supports that endocrine disrupting chemicals are associated with metabolic diseases like obesity and diabetes mellitus. The adipose tissue plays an essential role in those diseases and simultaneously it serves as storage of endocrine disruptors because of their lipophilic properties. The present article is a systematic review of the impact of endocrine disrupting chemicals on adipose tissue and suggests that exposure to them, in combination with other agents, may be crucial factor affecting adipogenesis.

**KEYWORDS**
endocrine disrupting chemicals, environment, adipose tissue

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## 1. INTRODUCTION

In recent years it has been recognized that adipose tissue participates not only in fat deposition, but also in energy homeostasis by secreting hormones and peptides [1]. Its accumulation is associated with many metabolic diseases like obesity, diabetes mellitus and atherosclerosis, which represent major health and economic problems [2].

Epidemiological evidence suggests that people of Westernized societies have considerably

higher percentage of adipose tissue indicating that changes in lifestyle and environmental impact may be crucial factors contributing to fat storage [3].

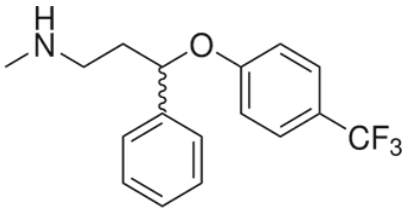
The present article is an overview of the available information linking EDCs with adipose tissue and suggests that exposure to them, in combination with other agents, may play essential role in adipocyte morphological characteristics.

## 2. ANTIMICROBIAL EFFICACY

The antimicrobial efficacy of Phenoxyethanol was also enhanced with the addition of the al-ternative blend Glyceryl Caprylate, Glycerin, Ca-prylyl glycol and Phenyl propanol in all the above cosmetic products (system III). In the case of body milk, because it is a leave-on product, an-other alternative preservative as Ethylhexyl glyce-rin was also tested (system IV).

The effectiveness of both systems III and IV against the examined bacteria and moulds is shown in Table II.

The action of all preservations systems used against *Aspergilus brasilliensis* is presented in Picture 1.




*Picture 1. Results of the challenge test regarding the activity of the preservative systems I - IV against Aspergilus brasilliensis in case of Body milk for children.*

The cosmetic products for children with the effective preservation systems II, III and IV were tested for their dermatological safety with a 48h patch test. The results showed that Phenoxyethanol combined with Chlorphenesin (system II) as a booster was dermatologically safe. The same results were achieved by the replacement of Chlorphenesin with alternative preservatives i.e. mixture of Glyceryl Caprylate, Glycerin, Caprylyl glycol and Phenyl propanol (system III) or Ethylhexyl glycerin (system IV) respectively, as a boosting system to Phenoxyethanol

## 3. DISCUSSION

Osteoporosis is a common disease characterized by a systemic impairment of bone mass and micro-architecture that results in fragility fractures. With an ageing population, the medical and socioeconomic impact of osteoporosis in general and postmenopausal osteoporosis in particular, will increase further [4,5,6].

Phenoxyethanol alone (system I) was used in cosmetic formulations for children because it is considered as both low-irritating and low-sensitizing preservative for personal care products. It is practically non toxical via oral and dermal use. It is not mutagenic in dermal studies. In clinical studies did not cause delayed hypersensitivity and was non-phototoxic. It is an excellent alternative to the standard, potentially harmful formaldehyde-releasing preservatives [4]. In our study it was proved efficient against *Pseudomonas aeruginosa*, *Escherichia coli*, *Candida albicans* but not for *Staphylococcus aureus* and *Aspergillus brasilliensis*. The lower action against *Staphylococcus aureus* is probably attributed due to its relatively high Minimum Inhibition Concentration (MIC=6400 ppm), whereas its MIC against other Gram(+) and Gram(-) bacteria is about 3200 ppm. The ineffective preservation against Aspergillus brasilliensis is probably caused by presence of glucan oligosaccharides in the products which may be a proper carbon-rich substrate for fungi growth. So, Phenoxyethanol in concentration 0.8 % w/w (system I) was not adequate according to European Pharmacopoeia as a preservative against all tested microorganisms for cosmetics of our series. Although, a higher concentration up to maximum (1% w/w) could be used, we thought that a combination of mixed preservatives at lower concentrations would be preferable in comparison to single preservatives, since the combination usually leads to products with lower toxicological potential and additionally, in some cases synergism could be achieved. Therefore, a second preservative with low toxicological profile as Chlorphenesin at concentration below than 0.5 % namely 0.1 % w/w was added to Phenoxyethanol (system II). Challenge tests proved that system II was effective against all examined microorganisms *Staphylococcus aureus* and *Aspergilus brasilliensis* included. So, the combination of the traditional preservatives Phenoxyethanol and Chlorphenesin was microbiologically effective (system II, Table II).

The toxicological potential of the system II was also tested by a 48h patch test in 20 subjects and the results showed that it was not irritant. Since we wanted to design products for children, we thought that the substitution of Chlorphenesin by an alternative preservative could be beneficial.

***Table II***
*Conventional established osteoporosis therapies*

| *Drugs* | *Anti-Fracture efficacy against Hip fractures & Vertebral fractures* | | *Side Effects* |
|---|---|---|---|
| Bisphosphonates | Anti-resorptive agents | Anabolic Agents | Osteonecrosis of the jaw, subtrochanteric femur fractures |
| Alendronate | Yes | No | Esophageal irritation |
| Risedronate | Yes | No | Esophageal irritation |
| Ibandronate | Yes | No | Esophageal irritation |
| Zoledronic acid18 | Yes | No | Hypocalcaemia, potential renal toxicity |
| Raloxifene | Yes | No | Thromboembolic disease |
| Strontium ranelate* | Yes | No | Thromboembolic disease; drug rash with eosinophilia systemic syndrome, abdominal discomfort |
| Teriparatide | No | Yes | Hypercalcaemia, nausea, diarrhea |
| PTH (1–84)** | No | Yes | Hypercalcaemia, nausea, diarrhea |

**Approved in over 70 countries, but not in the US,**Approved in Europe, but not in the US.*
Rachner T.D., Khosla S., Hofbauer L.C.: New Horizons in osteoporosis. *Lancet* 377 (9773): 1276-1287 (2011)

## 4. CONCLUSION

Osteoporosis is a global health problem, most common in women than in men, characterized by insidious loss of bone mass and strength.

Typically, it is associated with chronic pain, loss of autonomy, increased mortality in older patients, and vertebral, hip, proximal humerus, wrist and subchondral fractures of the femoral head.

With the variety of novel drugs that utilise the advanced knowledge of bone cell biology, has been expanded the armamentarium to facilitate the treatment of patients suffering from osteoporosis and other skeletal diseases.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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