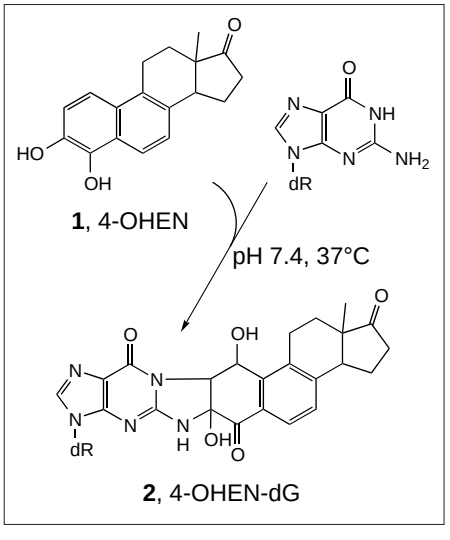
ERT cancer suspect?

The compound 4-hydroxyequilenin is a putative metabolite of Premarin, the oldest and most widely administered oestrogen replacement therapy (ERT) component (in the USA). According to Dr Judy Bolton and her colleagues at the University of Illinois (Chicago, USA) 4-hydroxyequilenin, *in vitro* at least, can attach to some of the basic building blocks of DNA and consequently may have important implications for hormone replacement therapy and the risk of cancer. They have recently reported their findings in the American Chemical Society journal *Chemical Research in Toxicology* [(1997) 10, 887–894].

Preliminary results

The researchers admit that the results of this new study are preliminary, but they could help clarify the link between ERTs and breast cancer, the cause of which has yet to be established. According to Bolton, a firm link between female reproductive variables and an increased risk of developing cancer in hormone-sensitive tissues, especially the breast, has been established from epidemiological studies. Exposure to oestrogens in women starts at menarche and ends at late menopause or continues with use of ERT, which may increase the risk of developing cancer. Almost a third of postmenopausal women in the USA receive ERT, and as the mean population age rises, decisions on whether to relieve menopausal symptoms, reduce the risk of cardiovascular disease and osteoporosis, and possibly stroke and Alzheimer's disease, must increasingly be weighed against the potential carcinogenicity of the therapy.



DNA adducts

Bolton and her team synthesized the catechol metabolite of Wyeth-Ayerst's Premarin 4-hydroxyequilenin (4-OHEN, **1**) – a semiquinone radical. They tested its reaction with the DNA base deoxyguanosine (dG) and found they could generate very unusual and unexpected products. The other bases dC and dA, but not dT, also became adducted. The structures of these adducts were determined by electrospray mass spectrometry and NMR experiments; for dG, this was found to be 2-N^1,3-N^2-deoxyguanosyl-1,3-dihydroxy-5,7,9(10)-estratriene-4,17-dione (**2**).

'If this reaction were to occur with DNA in breast cells,' Bolton explains, 'and that damage is not repaired, mutations could result, leading to the initiation of the carcinogenic process in the breast'. However, she emphasizes that they do not yet know whether this reaction actually takes place in cells, or in animals models *in vivo*, let alone in humans.

More research needed

There is a known direct link between long-term ERT and an increased risk of breast cancer. The potential for the formation of these reactive metabolites from all of the oestrogens in ERT formulations needs to be explored. The data suggest that several different types of DNA lesions could be expected from 4-OHEN including apurinic sites and bulky stable adducts, in addition to the previously known oxidized damage to DNA caused by 4-OHEN. The production of these semiquinone radical-derived DNA adducts could play a role in the carcinogenic effects of Premarin oestrogens. Bolton's team is currently carrying out work in cells to see if similar adducts are formed.

The FDA last year refused marketing approval for generic versions of Premarin until further research into their efficacy and safety had been reported.

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In short…

A new **Datamonitor** market report, *Market Dynamics to 2005: Schizophrenia*, highlights the serotonin-2 dopamine-2 antagonists (SDAs) as having the greatest potential in the schizophrenia R&D pipeline, with several products having now been launched. However, olanzapine (Zyprexa; **Eli Lilly**) is predicted to be the most successful long-term product.

The price of the full report is US$ 2,995 (see Web: www.datamonitor.com).

Following the successful achievement by **Xenova** of the pilot phase of the QTM™ drug discovery collaboration with **Parke-Davis** (a division of **Warner-Lambert**), their partner invested a further £1 million in March through a subscription for 457,584 shares in Xenova Group.

The project is a natural product screening collaboration, and the first compounds to be identified as potential leads were isolated and delivered to Parke Davis in 1997.

1359-6446/98/$19.00. PII: S1359-6446(98)01176-3