

# Northwestern University Medical School



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Larry G. Hart, MD  
111 Alexander Drive  
Building 101  
Research Triangle Park, NC 27709

RE: Human carcinogenicity of tamoxifen

Dear Dr. Hart:

I wish the committee to consider the following information regarding the carcinogenicity of tamoxifen, including the enclosed articles that I have published in the refereed literature at the invitation of the editors.

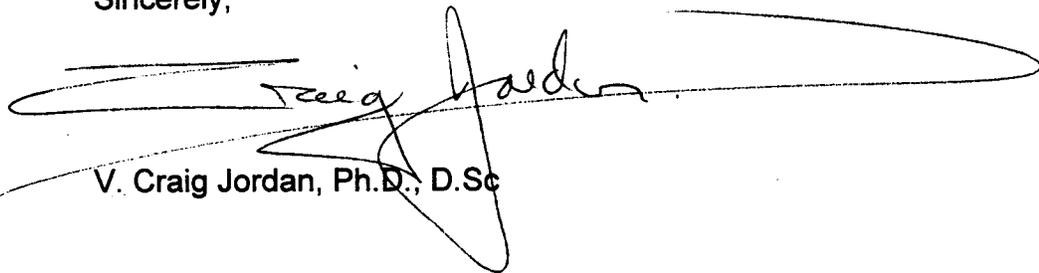
The issue for consideration is the proof of the carcinogenicity of tamoxifen in humans. In 1988 I published a caution (Gottardis et al 1988 Cancer Research 48:812-815) that patients with pre-existing endometrial cancer could have continued growth of their disease during adjuvant therapy for breast cancer. Our call resulted in the documentation of about 350 patients who had taken tamoxifen and developed endometrial tumors. This number is small compared with the world wide experience with the drug of millions of patients. It is consistent with the expected increase that would be observed with routine screening for endometrial cancer. We published our finding in several reviews and our conclusions were supported by the recent IARC press release (enclosed). Most importantly, our analysis (enclosed) of some of the published data was consistent with a model for the early detection of occult disease by excess sampling. This is considered to be an adequate explanation by the informed medical profession world wide. Indeed, the American College of Obstetrics and Gynecology does not recommend any special monitoring of tamoxifen treated patients because the actual incidence of endometrial cancer is very low, and routine screening is not cost-effective. It is quite clear that the benefits of the drug in reducing breast cancer mortality outweigh the risk of a small increase in endometrial cancer.

It seems unfortunate that a drug that has proved to be of such benefit to millions of women should continue to be investigated in a negative light. Clearly, the reason for the committees' actions should be of concern to the American people

as there is insufficient proof for the causation of endometrial cancer in humans. The animal data on rat liver carcinogenesis is not relevant or helpful and only serves to confuse the issue. Further efforts to undermine the public's confidence in a treatment deemed essential by the WHO, in the absence of a "safe" alternative, is counterproductive to the taxpayers of America and to the millions of women who are alive today because of the tamoxifen's benefits. Toremifene is being advocated by some as an alternative to tamoxifen.. Toremifene has not been FDA approved, and initial approval will be for advanced disease only. The committee cannot encourage Toremifene to be used widely without extensive clinical trial safety data. It would clearly be unethical to inadvertently create a situation that will jeopardize the health of women by encouraging them to use a "safe alternate drug" without adequate testing. This is extremely serious and the committee should not be involved in the marketing of fraudulent claims by the pharmaceutical industry. I must mention that the work I have recently completed in my laboratory shows Toremifene and tamoxifen to be equivalent in supporting the growth of human endometrial cancer under laboratory conditions. This will soon be published and our data forwarded to the FDA.

I would suggest to the committee that there is no basis for the assertion that tamoxifen causes endometrial cancer through initiation and decades of promotion. There is no safe alternative to the established agent, tamoxifen, that has improved the survival of millions of women with breast cancer. The classification of tamoxifen as a carcinogen in humans on the basis of abstract scientific principles has the potential to cause anxiety and harm to millions of American women.

Sincerely,



V. Craig Jordan, Ph.D., D.Sc



The following journal articles were attached to V. Craig Jordan's comments. Due to copyright infringement laws we cannot display them. We listed the citations for your information.

National Toxicology Program  
Report on Carcinogens Group

Assikis VJ, Neven P, Jordan VC, Vergote I. 1996. A realistic clinical perspective of tamoxifen and endometrial carcinogenesis. *Eur J Cancer* 32A(9):1464-1476.

Jordan VC, Morrow M. 1994. Should clinicians be concerned about the carcinogenic potential of tamoxifen? *Eur J Cancer* 30A(11):1714-1721.

Jordan VC. 1995. Tamoxifen and tumorigenicity: a predictable concern. *J Natl Cancer Inst* 87(9):623-626.

Jordan VC, Assikis VJ. 1995. Endometrial carcinoma and tamoxifen: Clearing up a controversy. *Clin Cancer Res* 1:467-472.

Jordan VC. 1995. What if tamoxifen (ICI46,474) had been found to produce rat liver tumors in 1973? A personal perspective. *Ann Oncol* 6:29-34.