NAMS
THE NORTH AMERICAN MENOPAUSE SOCIETY

March 1, 2002
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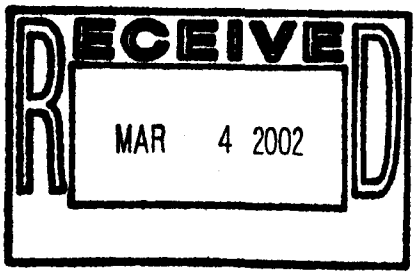


C. W. Jameson, PhD
NTP/NIEHS
79TW Alexander Drive
Building 4401, Room 3118
Research Triangle Park, NC 27709

Dear Dr. Jameson:

We submit this letter as a Task Force convened by the Board of Trustees of The North American Menopause Society (NAMS). NAMS is a nonprofit scientific organization dedicated to promoting women's health during midlife and beyond through the understanding of menopause. Its multidisciplinary membership of 2,000 leaders in the field – including clinical and basic science experts from medicine, nursing, sociology, psychology, nutrition, anthropology, epidemiology, and education – allows NAMS to be among the world's most trusted resources on all aspects of menopause to healthcare providers, researchers, and the public.

We commend the National Toxicology Program (NTP) for its ongoing mission to identify potential and known human carcinogens. However, we are concerned regarding its decision to include natural steroidal estrogens as "known human carcinogens" in the Tenth Report on Carcinogens.

The NTP's Clay B. Frederick, PhD, an invited speaker at the last Annual Meeting of The North American Menopause Society (October 3-5, 2001), encouraged us to submit our comments. At this conference, over 1,400 participants enjoyed the debate – "Estrogen Is/Is Not a Carcinogen" – in which Dr. Frederick presented the NTP's findings. We have been assured by Dr. Frederick and your office that our comments will be considered, although the deadline for comments has passed.

## COMMENTS

Including natural steroidal estrogens as "known human carcinogens" is a weighty step for the panel -- one that has great potential for harm to American women. **It should not be taken on the evidence presently available. The definition of a carcinogen that the NTP uses requires a causal relationship between the agent and human cancer. But, only an association with human cancer has been shown. Evidence of a causal effect remains unproven.**

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We have similar concern regarding the listing of several hormones in past editions as reasonably anticipated to be a human carcinogen" (eg, 17β-estradiol, progesterone) and "known to be a human carcinogen" (eg, components of conjugated estrogens).

We are concerned about the millions of women who may be confused, harmed, or alarmed by this action of the NTP. We respectfully ask the NTP not to declare steroidal estrogens as "known human carcinogens." In addition, we hope that endogenous human hormones (eg, 17β-estradiol, progesterone) will be reviewed for possible removal from the list of "reasonably anticipated to be a human carcinogen."

Should the NTP add steroidal estrogens to the list of "known human carcinogens," we urge consideration to using some type of grading scale. To place steroidal hormones on the same risk level as sulfites is inappropriate. Even putting diethylstilbestrol on the list does not meet the 1996 Federal guidelines as the relationship between DES and cancer has not been proven to be other than the disruption of the genital development program in such as manner as to open retained fetal genital cells to carcinogens.

To support our position, we offer the *Proposed Guidelines for Carcinogen Risk Assessment,* as published in the *Federal Register* on April 23, 1996 (Federal Register: 17960-18011) (copy attached). These are a revision of EPA's 1986 guidelines, as a better understanding of the actions of carcinogens had been obtained during the prior decade. We would like to call to your attention the following four points from the 1996 document:

> **Point 1.** *"The 1986 cancer guidelines have several limitations in addition to their inadequacy in addressing recent gains in the understanding of carcinogenesis. Although they called for the evaluation of all relevant information, the classification scheme used for identifying potential human hazard relied heavily on tumor findings, and in practice, seldom made full use of all biological information." ... "Hazard assessment emphasizes analysis of all biological information rather than just tumor findings."* Our comments on this point:
>
> This practice of not making full use of all biological information, and not disclosing it objectively, continued with the present report(s). **To date, no studies have unequivocally shown induction of any type of cancer by estrogens.**
>
> *A. Estrogen and Endometrial Cancer*
>
> Epidemiological studies generally show an association or relative risk, not causal relationships. No cause-effect relationship of estrogen to <u>any</u> cancer can be drawn from available epidemiological studies, and no attempts should be made to draw such conclusions. Therefore, all epidemiological studies quoted by the Committee are not interpretable by the NTP's own definition. To the contrary, steroidal estrogens and many other tested estrogen receptor ligands have never been shown by direct testing to be carcinogens. This includes both animal and human testing. Ergo, the risk of estrogen-induced cancer should be small – and it is.

The association between estrogen replacement therapy (ERT) and "endometrial cancer" is dubious. At the time of the initial reports of a relationship of ERT to endometrial cancer, it was stated repeatedly that the excess number of diagnosed cases were of low (nuclear) grade. The clear clinical difference between low nuclear grade endometrial cancer (LGED) and high nuclear grade endometrial cancer (HGEC) was not known. Both were thought to be part of the continuum toward a single entity; LGEC and HGEC were referred to as "low grade" and "high grade" endometrial adenocarcinoma, respectively. This is important because the diagnosis of extreme atypical hyperplasia vs. LGEC may be very subjective, and the biological outcomes are generally innocent.

In fact, LGEC and HGEC have different characteristics and outcomes, namely, LGEC almost always is estrogen-receptor positive (ER+), is hormonally responsive, rarely metastasizes, and is almost always cured by progestogen treatment or removal of the tumor in the uterus. In contrast, HGEC generally lacks estrogen receptors and is, therefore, insensitive to hormones, metastasizes early, and is often fatal if not diagnosed before metastases occur.

Since previously it was thought that one lesion blended into the other (LGE → HGEC), the main effort was placed on early diagnosis rather than separating the two entities. In fact, definitive early diagnosis of LGEC remains difficult since there is a continuum of benign hyperplasia, cytological atypia, and malignant change to be interpreted.

Since the addition of anti-estrogenic progestogens to ERT in women with intact uteri (the combination called hormone replacement therapy or HRT) obviates the occurrence of LGEC, progestogen use has become the clinical standard. The inflated number of diagnosed "endometrial cancers" has fallen and become of relatively small interest to gynecologists. But, the rate of HGEC has not diminished and its sporadic and uncommon occurrence have put HGEC "below the radar" of the methods being used to evaluate the question of HRT's effect on endometrial cancer. Nonetheless, a clue to this issue is found in the evidence that a woman using HRT at the time of diagnosis of "endometrial cancer" has no demonstrable different in lifespan as compared to non-ERT users.

Unfortunately, there have been few efforts to sort these matters out in light of the current understanding of endometrial cancer and there is no resolution to whether the association of estrogen with endometrial cancer (HGEC, to be precise) is causal or casual. Rather, ignorance has prevailed and few understand that only an association has been proven, **and that association is with LGEC and not HGEC.**

A few clinical trials of low-to-modest-dose ERT in women with uteri have begun to appear that show no increase in endometrial cancer. Hopefully, they will help spur the reconsideration of the relationship of ERT to endometrial cancer that is so long overdue.

As responsible clinicians, we are concerned about the potential association between unopposed estrogen and endometrial cancer that was suggested in past epidemiological

studies. These concerns led to advising cautious use of estrogen therapy in postmenopausal women with an intact uterus. We continue doing so until such time when well-controlled, prospective studies have established whether there is a link between endometrial cancer and contemporary estrogen therapy. However, the time-honored approach of adding anti-estrogenic progestogens to ERT is not based on biological evidence directly linking contemporary estrogen and endometrial cancer, since these data are lacking.

*B. Estrogen and Breast Cancer*

In order to understand the issues as they pertain to breast cancer, it is necessary to distinguish between the evidence associating locally-formed estrogen with breast cancer and the lack of evidence associating ERT/HRT with the incidence of breast cancer.

None of the epidemiological studies linking estrogen and/or progestogen treatment (ie, ERT/HRT) with breast cancer that were quoted by the Committee are biologically applicable to the NTP's definition of a carcinogen. There is more likelihood that the relationship of estrogen to breast cancer is in need of objective re-evaluation. In short, the contemporary evidence indicates that estrogen, but not ERT/HRT, is associated with adenocarcinoma for the breast. The nature of that association is not known. Evidence indicates that the local production of estrogen in the breast is the major determinant in that relationship. This casts doubt on the idea that the doses of hormone in contemporary ERT could be a material factor, if at all involved in the etiology of breast cancer.

The picture is further complicated by many issues, namely (1) the precise nature of the cancer(s) at issue is not known, (2) the length of residence of small numbers of malignant cells in the breasts and their trajectory through *in situ* to metastatic disease is not known, (3) the impact of rapid improvement of early diagnostic methods that has occurred during the same period, (4) the role of surviving past other diseases that might have claimed study subjects earlier, and (5) hormone effects on other systems in aging individuals.

At present, the available evidence shows: (1) improved prognosis if one is using ERT when the breast cancer is diagnosed, (2) that estrogens (including DES) are effective treatments for breast cancer, and (3) no increase is seen in recurrences of breast cancer in tumor-free women who receive ERT for symptoms. All are contradictory to the idea that ERT/HRT cause breast cancer and fit with the idea of a relationship including exposure of sensitive cells in the breast to factors leading to breast cancer, including locally formed estrogen.

*How the locally-formed estrogen is related:* The Committee apparently did not seriously consider the possibility that the issue of direct versus indirect actions of estrogen may be the result of activation of signaling cascades distal to the effect of estrogen, each of which can promote tumor progression by itself. Notable among them

are growth factors and oncogenes, all of which relate to cancer biology. At present, relatively little is known about cancer induction and initiation in general, and even less about the effects of estrogen. In the recent Committee report, recommendations were based on non-epidemiological studies, using animal models or tissue cultures. Conditions preclude drawing conclusions of direct cause-effect of estrogen. For instance, in experiments done in the presence of serum or oncogenes, the "cancer-promoting effect of estrogen" can be due to estrogen-induced increased sensitivity of the cell to the oncogene or simply the increased proliferation of cells that opens the genome to malignant transformation. Thus, an erroneous conclusion can be drawn that estrogen is a carcinogen, while in reality, oncogenes or other agents are the tumor initiators.

**Point 2.** *"Hazard characterization is added to integrate the data analysis of all relevant studies into a weight of evidence conclusion of hazard, to develop a working conclusion regarding the agent's mode of action in leading to tumor development, and to describe the conditions under which the hazard may be expressed (eg, route, pattern, duration, and magnitude of exposure)."* Our comments on this point:

Scientifically, it is hazardous to integrate data from different experiments into one body of a "working conclusion." In fact, a single well-designed study may have a greater biological significance than many weak studies. Combining data from a number of studies into meta-analyses has questionable scientific merit, and is dismissed *a priori* by knowledgeable scholars in biology and medicine.

However, this issue is even more complicated because in the path of revealing the "truth," one may often encounter conflicting results obtained from well-designed studies. For instance, two well-designed and well-conducted studies tested the same hypothesis, whether tamoxifen can prevent breast cancer, namely, the NSABP P-1 (Dunn BK, Ford LG. Breast cancer prevention: results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) breast cancer prevention trial (NSABP P-1:BCPT). *Eur J Cancer* 2000;36:S49-50) and the Royal Marsden Hospital trial (Powles TJ, et al. The Royal Marsden Hospital pilot tamoxifen chemoprevention trial. *Breast Cancer Res Treat* 1994;31:73-82). Interestingly, they came to entirely different conclusions.

Therefore, while no one single study may have monopoly over the "truth" of whether estrogen is a carcinogen, truth can be ascertained only when sufficient numbers of appropriate studies are conducted. As was stated above, at present no appropriate studies have been conducted to unequivocally determine the cause-effect of estrogen and cancer in humans.

**Point 3.** *The sections about "Dose response assessment is a two-step process" and "Three default approaches: Linear, nonlinear, or both."* Our comments on this point:

We understand from these paragraphs that the Committee's key argument is that of deriving secondary data (dose-response results) and turning it into prime evidence. This is similar to meta-analysis; by using secondary data from initially faulted or irrelevant studies, one cannot derive "stronger" conclusions.

**Point 4.** *"Descriptions of major default assumptions and criteria for departing from them are described." ... "Risk characterization is more fully developed by providing direction on how the overall conclusions and confidence of risk is presented for the risk manager. The Proposed Guidelines call for assumptions and uncertainties to be clearly explained."* Our comments on this point:

We assume that appropriate, objective, scientifically sound, self-criticism of the Committee's final statements has occurred. In support of such a serious and precedent-setting decision, these discussions should be presented for evaluation by the lay and medical public.

In addition, we have not seen the alternative hypotheses proposed by the Committee as to how estrogen could increase the risk of cancer. For instance, estrogen may prolong life and, thereby, the risk of cancer in women. The risk of breast cancer increases with age, and if a woman lives long enough, she increases her risk of developing breast cancer. Thus, it is possible that the increased incidence of breast cancer reported in some epidemiological studies of postmenopausal women treated with estrogen depends on longevity rather than on estrogen.

Another example: estrogen is a mitogen. Dividing cells, especially in older persons (both men and women), are more susceptible to *de-novo* chromosomal malfunctions that may lead to neoplasia. Therefore, it is possible that the increased incidence reported in some epidemiological studies of endometrial and breast cancer in postmenopausal women treated with estrogen depends on enhanced cell division, rather than on estrogen.

**In Conclusion**

In short, the evidence is that estrogen's relationship to the two most often cited cancers is that of an association, and not a causative effect. There is no evidence to indicate, much less confirm, that estrogen is a direct carcinogen. The argument of those in favor of using the association of a naturally-secreted hormone such as estrogen to identify those substances as carcinogens appears to be the beginning of a slippery slope which ultimately will lead to the identification of all mitogens as carcinogens.

While scientists who have great knowledge of the subject may comfortably disagree on whether estrogen is a carcinogen, imagine the burden that such a label places on the average woman who has natural exposure to a compound labeled as a carcinogen, or is considering ERT. Perhaps one day evidence will resolve this issue. Until then, surely we do a disservice to both our patients and our profession (clinicians and scientists) when we allow imprecision and selective observations to cloud the central evidence in these issues.

While ignorance may be a defense against our failure to fully resolve the role of estrogen in endometrial cancer and the effects that those reports had on women in the 1970s, the issues about which we are ignorant at this time are apparent. We must resist premature use of terms that likely will do greater harm than good. *"Primum non nocere"* is quite an apt motto in this issue.

The health consequences of the NTP's actions on these hormones are significant. Should you wish to continue this discussion, and/or should you wish a list of references for this material, please contact NAMS at 440/442-7550. Should you desire, we would also be pleased to provide an electronic file of this letter for posting on the NTB Web site.

Sincerely,

Carcinogen Task Force
The North American Menopause Society

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# Proposed Guidelines for Carcinogen Risk Assessment

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## ABSTRACT

Proposed Guidelines for Carcinogen Risk Assessment
EPA/600/P-92/003C
April 1996

The *Proposed Guidelines for Carcinogen Risk Assessment* were published in the *Federal Register* on April 23, 1996 (Federal Register: 17960-18011) for a 120-day public review and comment period. The Proposed Guidelines are a revision of EPA's 1986 *Guidelines for Carcinogen Risk Assessment* (51 FR 33992), and when final, will replace the 1986 cancer guidelines. The full text of the FR notice also is being made available via the Internet.

Since the publication of the 1986 cancer guidelines, there is a better understanding of the variety of ways in which carcinogens can operate. Today, many laboratories are moving toward adding new test protocols in their programs directed at mode of action questions. Therefore, the Proposed Guidelines provide an analytical framework that allows for the incorporation of all relevant biological information, recognize a variety of situations regarding cancer hazard, and are flexible enough to allow for consideration of future scientific advances.

The 1986 cancer guidelines have several limitations in addition to their inadequacy in addressing recent gains in the understanding of carcinogenesis. Although they called for the evaluation of all relevant information, the classification scheme used for identifying potential human hazard relied heavily on tumor findings, and in practice, seldom made full use of all biological information. Moreover, the conditions of the hazard were not taken into account. For example, it was common to assume that if an agent was carcinogenic by one route of exposure (e.g., inhalation), it posed a risk by any route. The 1986 cancer guidelines are also confined in that dose-response assessment allowed for only one default approach (i.e., the linearized multistage model for extrapolating risk from upper-bound confidence intervals). Moreover, very little guidance was given for risk characterization, the component of risk assessment that describes potential human risk, strengths and weaknesses of data, size of risk, and confidence of the conclusions for the risk manager. The Proposed Guidelines include the following changes to address these limitations, accommodate new information on carcinogenesis, and advance cancer risk assessment:

- **Hazard Assessment Emphasizes Analysis of All Biological Information** rather than just tumor findings.
- **Agent's Mode of Action is Emphasized** to reduce the uncertainty in describing the likelihood of harm and in determining the dose response approach(es). This emphasis should provide incentive for generating key information needed to reduce the default assumptions used in risk assessment.
- **Hazard Characterization is Added to Integrate the Data Analysis** of all relevant studies into a weight of evidence conclusion of hazard, to develop a working conclusion regarding the agent's mode of action in leading to tumor development, and to describe the conditions under which the hazard may be expressed (e.g., route, pattern, duration, and magnitude of exposure). (2)
- **Weight of Evidence Narrative Replaces the Current Alphanumeric Classification.** The narrative is intended for the risk manager and lays out a summary of the key evidence, describes the agent's mode of action, characterizes the conditions of hazard expression, and recommends appropriate dose response approach(es). Significant strengths, weaknesses, and uncertainties of contributing evidence are highlighted. The overall conclusion as to the likelihood of human carcinogenicity is given by route of exposure.
- **Three Descriptors for Classifying Human Carcinogenic Potential:** "known/likely", "cannot be determined", and "not likely" replace the six alphanumeric categories (A,B1,B2,C,D,E) in the 1986 cancer guidelines. Subdescriptors are provided under these categories to further differentiate an agent's carcinogenic potential.
- **Biologically Based Extrapolation Model is the Preferred Approach** for quantifying risk. It is anticipated, however that the necessary data for the parameters used in such models will not be available for most chemicals. The Proposed Guidelines allow for alternative quantitative methods, including several default approaches.
- **Dose Response Assessment is a Two Step Process.** In the first step, response data are modeled in the range of observation and in the second step, a determination of the point of departure or range of extrapolation below the range of observation is made. In addition to modeling tumor data, the new guidelines call for the use and modeling of other kinds of responses if they are considered to be measures of carcinogenic risk. (3)
- **Three Default Approaches—Linear, Nonlinear, or Both** are provided. Curve fitting in the observed range would be used to determine the effective dose corresponding to the lower 95% limit on a dose associated with 10% response (LED10). The LED10 would then be used as a point of departure for extrapolation to the origin as the linear default or for a margin of exposure (MOE) discussion as the nonlinear default. The LED10 is the standard point of departure, but another may be used if more reasonable given the data set [(e.g., a no observed adverse effect level (NOAEL)]. In support of discussion of the anticipated decrease in risk associated with various MOEs, biological information concerning human variation and species differences, the slope of the dose response at the point of departure, background human exposure (if known), and other pertinent factors would be taken into consideration.
- **Descriptions of Major Default Assumptions and Criteria for Departing From Them** are described. (4)
- **Risk Characterization is More Fully Developed** by providing direction on how the overall conclusion and confidence of risk is presented for the risk manager. The Proposed Guidelines call for assumptions and uncertainties to be clearly explained.

Document size: 495k
Number of tables: 0
Number of figures: 7

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*Updated January 7, 1999*