Food & Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Dear People: 5/25/00

I respectfully ask to be able to speak at the upcoming meeting regarding the Pill and the possibility of its over-the-counter use to be held on June 28 and 29th. Would you kindly inform me if you would allow me to speak and if so, for how long, as I would need to take a day off of work and come down to Washington. I submit the handout from which I would make my comments.

Thank you

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flyer submitted: *Overview: Breast Cancer and the Pill*

OVERVIEW: BREAST CANCER AND THE PILL

Q-2A: What is an oral contraceptive?

An oral contraceptive is usually a combination of a synthetic estrogen and progestin (ie, the two major types of female hormones) which women take for 21 days out of a 28-day cycle. These hormones work by suppressing, but not eliminating ovulation, thickening cervical mucus, and by changing the lining of the uterus.

Q-2B: Is there any evidence that the OCP (oral contraceptive pill) causes breast cancer in animals?

Yes. Concerns were raised in 1972 when it was noted that an oral contraceptive pill containing the artificial hormones mestranol and norethynodrel appeared to cause a case of metastatic breast cancer in a female rhesus monkey [252]. This was especially worrisome since rhesus monkeys rarely develop breast cancer. Until that time, only three cases of breast cancer in rhesus monkeys were reported. Although some argued that this was simply a "chance finding," concern grew further when it was noted that both beagles and rodents developed breast cancer when exposed to the hormones contained in today's OCPs [sources: 267, 268, 255, 313, 254].

Q-2C: How might OCPs cause breast cancer in humans?

In 1989, Anderson et al [174] published a classic paper regarding the influence of the OCPs on the rate of breast cell division. They found that nulliparous women (ie, women who have not had children) who took OCPs had a significantly higher rate of breast cell division than nulliparous women who did not take them. This was especially important since it is known that in general, cells which divide more rapidly are more vulnerable to carcinogens (ie, cancer producing agents) and thus more likely to become cancerous.

Q-2D: Do oral contraceptives cause an early abortion and if so, could this also be playing a role in the increased risk of breast cancer?

It is conservatively estimated that a woman who takes the oral contraceptive pill (OCP) will have at least one abortion for every year that she is on it [251]. Both pro-life and pro-abortion groups openly admit that OCPs cause early abortions, with the latter doing so publicly in testimony before the Supreme Court in 1989 {*The New York Times*} [157]. Induced abortion before a woman's first-term pregnancy has been noted to increase a woman's risk of breast cancer by 50% [98]. Could an abortion within the first week of conception have a deleterious effect as concerns breast cancer? The hormonal physiology of early pregnancy is difficult to measure but Stewart et al [240] and Norman et al [361] have shown that estradiol and progesterone levels (ie, the female hormones) start to rise above baseline levels within four days of conception, thus prior to implantation and before HCG levels begin to rise. An early abortion would cause a sudden fall in the levels of these hormones. Could this early "hormonal blow" be playing a role? To this author's knowledge, no one has asked or studied this question.

Q-2E: Can you give a brief history of the studies that showed a link between the risk of taking OCPs prior to first term pregnancy and the increased risk of breast cancer?

In 1981, Pike et al [138] found that women who took OCPs for four years before their first term pregnancy had at least a 2.25 fold increased risk of developing breast cancer before age 32. This startled the research world and led to additional studies, including a very large American trial called

the CASH study (ie, Cancer And Steroid Hormone study). In 1993, the CASH study showed that women who took OCPs prior to first term pregnancy and were under 44 years of age had a 40% increased risk in breast cancer, which reached statistically significance in the 35-44 age group [6].

Later in England, Chilvers et al [8] published the results of another large study called the United Kingdom National Study. She showed that young women under the age of 36 who had used oral contraceptives for at least 4 years before their first term pregnancy had at least a 44% increased risk in breast cancer. The last large study was performed in 1995 by Brinton et al [1]. It showed a 42% (raw relative) increased risk for women who used OCPs for more than 6 months prior to having a full term pregnancy.

Q-2F: If the major studies showed the risks that have been mentioned, then why do doctors and pharmacists fail to inform their patients of those risks?

That is a good question. Major journals and major medical associations (eg, the AMA {American Medical Association}, ACOG {American College of Obstetricians and Gynecologists}, and the AAP {American Academy of Pediatrics}) have failed to stress or properly note this risk. Part of the problem is that because the OCP/breast cancer debate is complicated, most lay people have to rely on what "the experts" tell them.

A good example of this occurred recently in the Oxford study reported in condensed version in *The Lancet* [257] and in complete form in *Contraception* [258]. This study was and remains the largest meta-analysis (ie, a synthesis of all the major studies done in a particular field, concluding in an overall risk for the pooled studies) regarding the studies of OCPs and breast cancer. Researchers from around the world studied and combined the data from 54 studies, involving 25 countries and 53,297 women who had breast cancer. It concluded that: "Women who are currently using combined oral contraceptives or have used them in the past 10 years are at a slightly increased risk of having breast cancer diagnosed, although the additional cancers tend to be localized to the breast. There is no evidence of an increase in the risk of having breast cancer diagnosed 10 or more years after cessation of use..." Unfortunately, this study is known more for what it did say, than what it did not say! There were ***several major weaknesses*** of the study.

Q-2G: What are the **weaknesses** of the Oxford study and what implications do they have?

The main weakness was the failure to report any evidence of what the pooled risk of oral contraceptive use before a first term pregnancy was in women less than 45 years old. Another major weakness is that the Oxford study pooled data from studies which looked at women with breast cancer from the early and mid 1970s [258, p5S].

A woman's breast is especially sensitive to carcinogenic influence (ie, cancer producing influence) *before* she has her first child since the breast undergoes a maturing process throughout a woman's first pregnancy. By failing to measure the effect of OCP use *before* a woman's first term pregnancy (FTP), the Oxford study failed to give data on the one group of women who are most likely to get breast cancer from oral contraceptives, namely, those women who used them before their first term pregnancy (eg, many teenagers and women in their twenties).

The second weakness is that the Oxford study used data from older studies which took some of their data from the mid and early 1970s. This does not leave a long enough latent period. A latent period is the time between exposure to a suspected risk factor (eg, early OCP use) and the cancer which it increases (eg, breast cancer). Often the latent period between a risk factor and a cancer is 15 to 20 years or more (eg, cigarettes and lung cancer). Although women in the US began taking OCPs in the 1960s, they only began taking them for longer periods of time at younger ages in the 1970s. Thus, only studies which include data from the 1980s and 1990s or beyond would allow a long enough latent period to pick up the influence of early OCP use.

Q-2H. What do the four largest retrospective studies**, which take the bulk of their data after 1980, state regarding women who used OCPs prior to first term pregnancy (FTP)?

Table 2A: RISK OF BREAST CANCER IN WOMEN WITH OCP USE PRIOR TO FIRST BIRTH

AUTHOR	YEARS STUDIED	SIZE OF STUDY	*FINDINGS*
Wingo [6] CASH Study	12/80-82	2089 less than age 45	**40% raw increase; ages 20-44**
Rosenberg [28A]	1977-1992	1427 less than age 45	**88% raw increase***
White [35]	1983-1990	747 less than age {Parous women}	**50% increase: for use within 5 years of menarche**
Brinton [1]	5/90-12/92	1648 less than 45 years old	**42% increased risk***

*Computed from raw data from study, increase reflects the raw relative risk

**[An example of a retrospective study is one in which women with breast cancer would be interviewed and asked questions about their risk factors such as family history, OCP use, induced abortion, etc.]

The four largest studies of women under the age of 45 all show at least a 40% increased raw relative risk for women who took OCPs prior to their FTP or within five years of menarche. Two studies (Rosenberg and Brinton) did not list a formal risk but it was calculated from the data in their paper.

Q-2I. Has anyone done a meta-analysis that examined the question of risk in women under age 45 who had taken OCPs prior to full term pregnancy?

Yes. Two different researchers have addressed this question. Thomas et al, in 1991, found that women who took OCPs for extended periods of time prior to FTP had a 42% increased risk [184]. A more refined meta-analysis in 1990 by Romieu et al restricted her analysis to those studies done after 1980. The study showed that women under age 45 who had taken OCPs for four or more years prior to FTP had a 72% increased incidence [RR=1.72 (1.36-2.19)] of breast cancer [55].

Q-2J. Can you give an overall statement regarding early OCP use and breast cancer?

Yes. If a woman takes the oral contraceptive pill before her first child is born, she suffers a 40% increased risk of developing breast cancer compared to women who do not take the pill. If she takes OCPs for four years or more prior to her first baby, she suffers at least a 72% increased risk for developing breast cancer.

Q-2K. Are any other groups of women at high risk?

Yes. Women who take OCPs for a **long periods of time** (ie, four years or more) [8,26,34], are at increased risk for developing breast cancer. Other women at risk are **those who use them after age 25** [18,30,33] and **nulliparous women** who use them for a long time (ie, four or more years) [8,27]. All three categories of women seem to be at increased risk, with individual studies ranging from 40% to over 200% increased risk. Women who took OCPs for longer time periods and started using them

at an early age appear to be at an even greater risk. *For example, the Brinton study [1] is significant in that she allowed a longer latent period to pass and found a 210% increased risk of developing breast cancer in young women (ie, under age 35) who took OCPs for more than 10 years, if they began taking them before age 18 [RR=3.1 (1.4-6.7)]*.

Q-2L: It has been noted that OCPs reduce the rate of uterine and ovarian cancer. Is this true?

Yes, it is true. However it must be noted that OCPs also increase the risk of cervical and liver cancer [215A, 215B, 264]. For example a weighted analysis (see chapter 13) has noted that women who have taken OCPs prior to age of 20 have an 80% increased risk of developing invasive cervical cancer [215A, 223A, 223B, 227, 229, 229B]. In addition, more women get breast cancer in the US, than all of the other alluded to cancers combined, making this the most dangerous risk in western countries. Oral contraceptives may be particularly risky in **Asian and African countries where liver cancer is extremely prevalent** [301, p579].

Q-2M: Often women who have painful menstrual cycles are placed on OCPs. Are there medical alternatives with less risks than the OCP?

Menstrual cramps can be controlled by other less harmful drugs called non-steroidals such as naproxen or ibuprofen, alone, or in combination with acetominophen. Other doctors treat cramps by encouraging women to take 1,000 mg of calcium 400 mg magnesium directly before and during menstruation. Conversely, *The Journal of Adolescent Medicine* published a case report of a young lady who experienced a 90% reduction in her cramping symptoms when taking nicardipine for relief of her menstrual cramps [344]. Nicardipine is a type of calcium channel blocker that is used for treating hypertension.

Q-2N: What about the risk of "low dose" progestin containing contraceptives such as "the minipill," or long-acting progestins such as Norplant or Depo-Provera?

Skegg et al [163] pooled the data from the WHO (World Health Organization) and New Zealand studies, *the two largest studies that looked at women who took Depo-Provera* (active ingredient is DMPA: depo-medroxyprogesterone acetate) for long periods of time. He found that women who had taken DMPA for between two and three years before age 25 had a 310% statistically significant risk of getting breast cancer {RR=4.1: (1.6-10.90} while women who had taken DMPA for more than 3 years prior to age 25 had at a 190% increased risk, that was also significant {RR=2.9: (1.2-7.1)}. The risks for long-term Norplant use in young women could be just as dangerous as those of Depo-Provera although widespread tests have not been done because Norplant was developed later than Depo-Provera.

Q-2O: How do the natural means of regulating birth compare to the artificial means?

Several well-designed trials by the World Health Organization have shown that Natural Family Planning (NFP)* (ie, a method of determining when a woman is most fertile or infertile, based on using natural means such measuring the thickness of a woman's cervical mucus, some NFP users advocate measuring basal body temperatures as well) has had an effectiveness rate that is on par with

[*for more information regarding NFP see end of bibliography]

OCPs—that is, less than 3% pregnancies per year. These trials have been done in both modern and less advanced countries and have shown low annual pregnancy rates: the United Kingdom—2.7% [280], Germany—2.3% [281], Belgium—1.7% [282], and India—2.0% [283]. *In addition, one of the largest trials of 19,843 women performed by the World Health Organization in India showed the failure rate to be 0.2 pregnancies per 100 women yearly—a rate that is certainly comparable to artificial methods of contraception* [286].

Q-2P: How can I verify the above noted information?

Go to your nearest medical library—nearly every hospital has one—and ask the librarian to help you look up the medical references that interest you.

252 Kirschstein RL et al. Infiltrating duct carcinoma of the mammary gland of a Rhesus monkey after administration of an oral contraceptive: a preliminary report. *JNCI*; 48: 551-553.
267 Geil et al FDA studies of estrogen, progestogens, and estrogen/ progesterone combinations in the dog and monkey. J Tox. Env. Health. 3: 1979.
268 Shubik P. Oral contraceptives and breast cancer: laboratory evidence. In: Interpretation of Negative Epidemiological Evidence for Carcinogenicity. *IARC* Sci. Publ. 1985: 65; 33.
255) Kahn RH et al Effect of long-term treatment with norethynodrel on A/J and C3H/Hej mice. *Endocrinology* 1969; 84: 661.
313) Weisburger JH et al Reduction in Carcinogen Induced Breast Cancer in rats by an anti-fertility drug. *Life Sci.* 1968; 7: 259.
254) Welsch CW et al 17B-Estradiol and enovid mammary tumorogenesis in C3H/HeJ female mice: counteraction by concurrent 2-bromo-ergo cryptine. *Br. J. Cancer.* 1977; 35: 322
174 Anderson T, Battersby S, et al Oral contraceptive use influences resting breast proliferation. *Hum Pathol.* 1989; 20: 1139-1144.
251 Kahlenborn C How do the pill and other contraceptives work? *Life Advocate*. July 1997; 20-25.
98 Brind J, Chinchilli M, Severs W, Summer-Long J. Induced abortion as an independent risk factor for breast cancer: a comprehensive review and meta-analysis. *J. Epi. and Comm. Health.* 10/ 1996; 50: 481-496.
240 Stewart DR, Overstreet JW, et al Enhanced ovarian steroid secretion before implantation in early human pregnancy. *J of Endo. and Met.* 1993; 76: 1470-1476.
138 Pike MC, Henderson BE, et al Oral contraceptive use and early abortion as risk factors for breast cancer in young women. *British Journal of Cancer* 1981; 43: 72-76.
6 Wingo PA, Lee NC, et al Age-specific differences in the relationship between oral contraceptives use and breast cancer. *Cancer* (supplement). 1993; 71: 1506-17
8 Chilvers C, McPherson K, et al Oral contraceptive use and breast cancer risk in young women {UK National Case-Control Study Group}. *The Lancet*. May 6, 1989: 973-982.
1 Brinton LA, Daling JR et al Oral contraceptives and breast cancer risk among younger women. *JNCI*. 6/7/1995; 87: 827-35.
257 Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies. *The Lancet* 1996; 347: 1713-1727.
258 Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: further results. *Contraception*. 1996; 34: S1-S106.
28A Rosenberg L, Palmer JR, et al Case-control study of oral contraceptive use and risk of breast cancer. *American Journal of Epidemiology*. 1996; 143: 25-37.
35 White E, Malone K, Weiss N, Daling J. Breast cancer among young US women in relation to oral contraceptive use. *JNCI*. 1994; 86: 505-514
184 Thomas DB Oral contraceptives and breast cancer: review of the epidemiological literature. *Contraception*. 1991; 43: 597-642
55 Romieu I, Berlin J, et al Oral contraceptives and breast cancer. *Cancer*. 1990; 66: 2253-2263

26 Rookus MA, Leeuwen FE. Oral contraceptives and risk of breast cancer in women ages 20-54 years. *Lancet*. 1994; 344: 844-851.
34 Weinstein A, Mahoney M, et al Breast cancer risk and oral contraceptive use: results from a large case-control study. *Epidemiology*. 1991; 2: 353-358.
18 Palmer J, Rosenberg L, et al Oral contraceptives use and breast cancer risk among African-American women. *Cancer Causes and Control*. 1995; 6: 321-331.
30 Thomas DB, Noonan EA. Breast cancer and combined oral contraceptives: results from a multinational study [The WHO collaborative study of Neoplasia and steroid contraceptives]. 1990; 61: 110-119.
33 Wang Q, Ross R, et al A case-control study of breast cancer in Tianjin, China. *Cancer Epidemiology*. 1992; 1: 435-439.
27 Miller D, Rosenberg L, et al Breast cancer before age 45 and oral contraceptive use: new findings. *American Journal of Epidemiology*. 1989; 129: 269-279.
85 Colton T, Greenberg ER, et al Breast cancer in mothers prescribed diethylstilbestrol in pregnancy. *JAMA*, 1993; 269: 2096-3000.
215A Thomas DB et al Oral contraceptives and invasive adenocarcinomas and adenosquamos carcinomas of the uterine cervix. *American J. of Epidemiology*. 1996; 144: 281-289.
215B Ebeling K. et al Use of oral contraceptives and risk of invasive cervical cancer in previously screened women. *Int J. of Cancer*. 1987; 39: 427-430.
264 Kenya PR. Oral contraceptive use and liver tumours: a review. East African Medical Journal. 1990. 67 146-153.
301 Fauci AS et al Harrison's: Principle of Internal Medicine 14th edition. McGraw Hill Inc. NY.(C) 1998.
344 Earl DT, et al. Calcium channel blockers and dysmenorrhea. *Journal of Adolescent Medicine*. 1992; 13: 107-108.
163 Skegg DCG, Noonan EA, et al Depot medroxyprogesterone acetate and breast cancer [A pooled analysis of the World Health Organization and New Zealand studies]. 1995; *JAMA*: 799-804.
175 Croxatto HB, Diaz S, et al. Plasma progesterone levels during long-term treatment with levonorgestrel silastic implants. *Acta Endocrinologica* 1982; 101: 307-311.
280 Clubb EM et al A pilot study on teaching NFP in general practice: current knowledge and new strategies for the 1990s. Washington, DC Georgetown University, 1990: 130-132.
281 Frank-Hermann P et al Effectiveness and acceptability of the symptothermal method of NFP in Germany. *Am. J. of Obstet. Gyn.* 1991; 165: 2052-45.
282 Liezola MA. De premiere d'une etude prospecive d'efficacite du planning familial naturel realisee en Belgique francophone. *J. Gyncol. Obstet. Biol. Rev.* 1994, 23: 359-364.
283 Dorairaj K. The modification mucus method in India. *Am J. Ob. Gyn.* 1991; 165: 2066-67.
286 Ryder RE. "Natural Family Planning": Effective birth control supported by the Catholic Church. *BMJ*. 1993; 307: 723-6.
355) Hankinson SE et al A prospective study of oral contraceptive use and risk of breast cancer (Nurses Health Study, United States). *Cancer Causes and Control*. 1997; 8: 65-72.

For more information on NFP call or write to:

- The Couple to Couple League
  PO Box 111184
  Cincinnati, Ohio 45211-1184
  1-513-661-7612

- Pope Paul VI Institute at 1-402-390-6600 or write to:

- Family of the Americas
  1-800-443-3395
  www.familyplanning.net.
  e-mail: family@upbeat.com