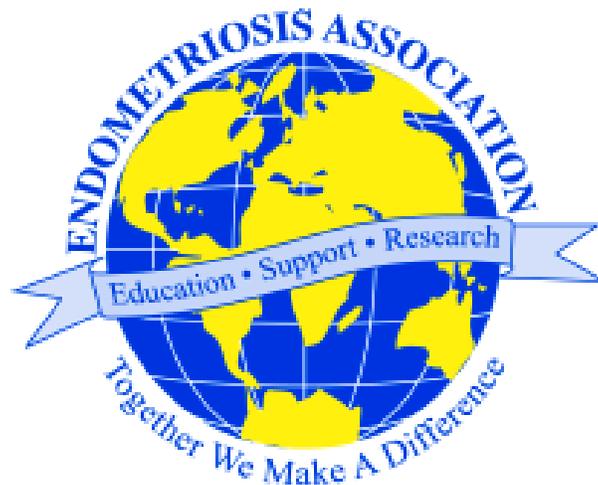


ENDOMETRIOSIS & DIOXINS

**Information for physicians, nurses, and
other healthcare professionals**



Endometriosis Association
International Headquarters
8585 North 76th Place
Milwaukee, Wisconsin 53223 USA

(414) 355-2200
(414) 355-6065 fax
Endo@EndometriosisAssn.org
www.EndometriosisAssn.org

The Endometriosis Association is a self-help organization of women and families with endo, doctors and scientists, and others interested in exchanging information about the disease, offering mutual support and help to those affected by endo, educating the public and medical community about the disease, and promoting research related to endo.

With headquarters based in Milwaukee, Wisconsin (USA), the Endometriosis Association consists of members, chapters, and activities worldwide. Elected officers guide the organization, consulting with an advisory board of medical professionals and other dedicated individuals. Founded in 1980 by Mary Lou Ballweg and Carolyn Keith, the Association was the first group in the world dedicated to helping women with endometriosis.

The Association's Research Program includes the world's largest endometriosis database, a major research partnership with Vanderbilt University School of Medicine, collaboration with the U.S. NIH, and funding of promising research worldwide. The Association also serves as a clearinghouse for information on the disease and provides a range of support services for those with endometriosis.

What You Can Do

There is still much to learn about the causes of endometriosis, diagnosis, treatment, management, and even prevention of the disease. Join the Endometriosis Association. The Association's core of both patient advocacy and science helps build a strong bridge between women and girls with endometriosis and their healthcare providers.

This brochure was made possible in part through funding from the Beldon Fund and New York Community Trust.

© Copyright 1998, 2004, 2007, 2009 Endometriosis Association.

All rights reserved

ENDOMETRIOSIS & DIOXINS

Information for physicians, nurses, and other healthcare professionals

The Environmental Protection Agency (EPA) stated in its *Draft Dioxin Reassessment* (1994) that the "general population's current body burdens and exposures of dioxin are already at levels which affect our health." One of the health effects EPA specifically identified was "a higher probability of experiencing endometriosis and the reduced ability to withstand an immunological challenge."¹

Incidence Is Rising Dramatically.

Doctors have puzzled over why incidence of endometriosis, which was considered relatively rare even in the early 1980s, has been skyrocketing. Affecting at least 7.5 million women and girls in the United States and Canada, it afflicts millions more worldwide. Endometriosis is a disease of the endocrine and immune systems in which tissue similar to the endometrial tissue of the uterus occurs abnormally in other areas of the abdomen.² Infertility afflicts 30% to 40% of women with endometriosis and is very common with progression of the disease.³

Advances in diagnosis and reporting do not explain the current epidemic rates of endometriosis. Greater awareness fails to explain documented increased rates of hysterectomies due to endometriosis, most notably in teenage girls. According to data from the U.S. National Center for Health Statistics, and analysis by Dr. Gary Berger (Medical Director, Chapel Hill Fertility Center), hysterectomies for endometriosis increased 250% for young women between the ages of 15-24 and 186% between the ages of 25-34 during 1965 to 1984.⁴

Earlier age of onset, increasing severity

Results of a 1998 study by the Endometriosis Association, presented at the VI World Congress on Endometriosis, provided startling data about the disease.⁵ Mary Lou Ballweg, Association President, and Bob Fichtner, statistician, analyzed data on 4000 North American women with diagnosed endometriosis. On average it took 9.28 years for women to receive a correct diagnosis of endometriosis. The study also revealed that the earlier the onset of symptoms, the greater the length of time before diagnosis, and the wider the variety of symptoms young women experienced. Those with symptoms as teenagers were more likely to suffer disability from the disease—a significant fact, considering that 66% reported having initial symptoms before age twenty. The data suggest that more girls may be experiencing more severe symptoms at younger ages.

There is growing concern that hormonally active chemicals, such as dioxins and other chemicals that mimic hormones or cause other dysfunctions in the endocrine and immune systems, are accelerating the onset of puberty. According to a recent study in the *Journal of Pediatrics*, girls in the United States are reaching puberty earlier than ever. Nearly half of African American girls and 15% of Caucasian girls are beginning to develop sexually at the age of eight. Development of breasts and pubic hair were two of the characteristics occurring at significantly younger ages than previously.⁶ The authors of the study called for more investigation into whether hormonally active chemicals (which are more prevalent in communities of color⁷) are responsible for these findings.

Greater range of symptoms

A far more complex and sophisticated understanding of the disease has developed in recent years, including the recognition of a range of symptoms associated with endometriosis (see chart).

Symptomatology of Endometriosis

	<i>% of total</i>
Dysmenorrhea and/or pain throughout cycle	95
Fatigue, exhaustion, low energy	87
Diarrhea, painful bowel movements, or other intestinal upsets w/menses	83
Abdominal bloating	84
Heavy or irregular periods	65
Dyspareunia (painful sexual intercourse)	64
Nausea, stomach upset at time of menses	64
Dizziness, headaches w/menses or pain	63
Low resistance to infections	43
Infertility	41
Low-grade fever	32
No symptoms	1

(Based on 4000 case histories in the Research Registry of the Endometriosis Association)

What Are Dioxins?

According to the EPA, dioxins are the most potent synthetic carcinogens yet tested.⁸ Dioxins are a class of chemicals with similar properties; these include the parent compound—2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD)—and certain types of *chlorinated dibenzodioxins*, *dibenzofurans*, and *polychlorinated biphenyls (PCBs)*. Whereas PCBs are man-made (and act like dioxin in the body and *bioaccumulate*), dioxins are an accidental byproduct of a multitude of industrial processes in which chlorine is present, such as municipal and medical waste incineration, chemical and plastics manufacturing, pesticide and herbicide production, and pulp/paper bleaching.⁹

Major sources of exposure

Once created, dioxins concentrate dramatically in the food chain. Dioxins contaminate beef, fish, poultry, and dairy products. Animals consume pesticide- and herbicide-laden food, and humans consume animals and fish, our primary exposure to dioxin.¹ Dioxins are measured in fish at levels up to a million times greater than those found in the surrounding water. The remainder of human exposure occurs from contaminated air, water, and bleached paper products.

Menstrual hygiene products and exposure?

According to the U.S. Food and Drug Administration (USFDA), tampons and sanitary pads made of rayon or bleached cotton contain low levels of dioxins.¹⁰ The USFDA allays concern about chemicals in these products by asserting that levels at parts per trillion are so low that risk is minimal.¹⁰ EPA tests, however, assert that dioxin levels once thought acceptably low, adversely affect the reproductive and immune systems.^{8,11}

Tampon safety legislation, introduced in Congress in January 2003 (H.R. 373, Carolyn B. Maloney, 14th District, New York) would direct the National Institutes of Health (NIH) to research health risks to women—including endometriosis and cancers of the breast, ovaries, and cervix—from the presence of dioxin, synthetic fibers, and other additives in feminine products.^{12,13} Until research addresses the risks, health experts recommend unbleached, organic cotton sanitary pads and tampons (without plastic applicators).¹⁴

Bioaccumulation in the body

In the process of bioaccumulation, dioxin, even in very low doses, builds up in the body over time, as it concentrates in fatty tissues. Dioxin also *biomagnifies* through the food chain as higher organisms consume plants and small animals.² According to the EPA, the half-life of TCDD in the body (the time to rid the body of half of the amount of bioaccumulated dioxin) is about seven years, while the half-life of PCBs is variable.^{2,15,16}

“¹⁹It is possible for a woman to excrete half of her accumulated amount of dioxin during lactation.”

In general, our body burden of dioxins increases as we get older. The time of exposure to TCDD during our lives may also affect our body burden of dioxin as adults. A recent study (Seveso, Italy) showed that girls younger than age 10, who were exposed to dioxin, retained higher levels of dioxin later as adults, as compared to women not exposed until teen or adult years.¹⁷

Studies have shown that humans and wildlife are exposed to a myriad of dioxin chemicals. How do we determine our total exposure to dioxins? The toxicity of individual dioxin-like chemicals is assessed using a toxic equivalency

approach. Based on all available studies, chemicals that are dioxin-like are assigned a relative potency factor that expresses their toxicity in relation to that of TCDD. The total toxic TCDD equivalency quotient (TEQ) is the sum of the amount of each chemical present in a biological sample, times its individual TEF. Thus, the total body burden of dioxins present in our blood is measured as total serum TEQ. It is important to consider the total TEQ of dioxins in assessing the health risk of exposure, rather than TCDD alone. In the general population, TCDD contributes approximately 15% of the body burden of dioxins, while dibenzodioxins, dibenzofurans, and PCBs constitute about 85% of the dioxin body burden.¹⁸

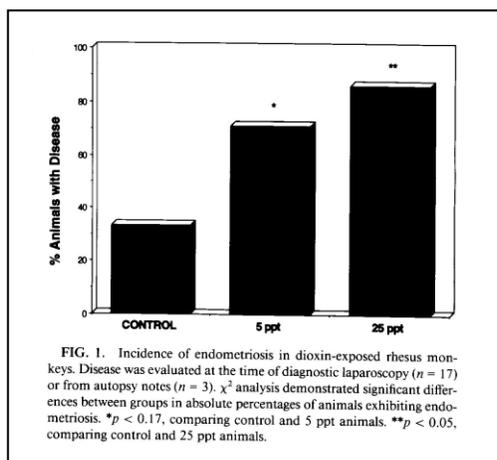
Gynecologists and other physicians are already aware of the effects of prenatal exposure to hormones, such as the synthetic estrogen, diethylstilbestrol (DES), and that the prenatal and neonatal stages are critical times of development and sensitivity to toxic chemicals. A multi-generational effect of embryonic exposure to dioxin has now been shown in an animal model of endometriosis.⁵⁹ It is possible for a woman to “excrete half of her accumulated amount of dioxin during lactation.”¹⁹ Dioxins have been found in breast milk worldwide—the highest concentrations in industrialized countries.²⁰

Behavior of dioxins in the body

Dioxins interfere with the cell's gene processes. Entering a cell, dioxins bind to the aryl hydrocarbon receptor protein, or AhR, which is present in many parts of the body including liver, lungs, lymphocytes, and placenta.²¹ Once bound to the AhR, dioxins can move freely inside the cell, and when binding to DNA inside the nucleus, they are able to switch genes on and off.^{21,22} The genes targeted by dioxins influence hormone metabolism and growth factors, and thus affect reproduction, endocrine, and immune functions.^{9,22}

Dioxin Exposure and Endometriosis

A 1992 study analyzed rhesus monkeys exposed for four years to 5 ppt and 25 ppt of TCDD, the most toxic form of dioxin.²³ Association researchers concluded that “the incidence of endometriosis was directly correlated with dioxin exposure and the severity of disease was dependent upon the dose administered.”²³ This study demonstrated that “chronic exposure to the chemical toxin dioxin is directly correlated with an increased incidence in the development of endometriosis in rhesus monkeys.”²³



In addition to these findings, the dioxin-exposed monkeys showed immune abnormalities and altered GI microflora similar to those observed in women with endometriosis.⁶¹ Dioxins adversely affect production of cytokines known to participate in the regulation of uterine physiology.^{22,24,25,26,27,28,63} Dioxins “turn on” genes that promote inflammation and disrupt normal growth processes that may lead to the development and progression of endometriosis.^{51,64} Uterine endometrium and endometriotic lesions express the genes for the AhR, and studies suggest that these tissues are targets for dioxin action. A recent report demonstrates that exposure of endometrium and endometriosis tissues to a combination of 17β -E₂ and TCDD increases the expression of growth factors

and receptors involved in allergic inflammation (I-309-CCR8).⁶² An excellent review of dioxin's

inflammatory properties ties together many of the steps from exposure (which may be embryonic) to full-blown endometriosis.⁶⁵ Dioxins also modulate various hormone receptor systems that play a role in uterine function.^{23,29,30}

Research utilizing a rodent model further supports the 1992 findings, by demonstrating that “administration of TCDD to rats and mice also resulted in the promotion of the growth of endometriotic sites.”³¹ The rats demonstrated endocrine dysfunction and subtle tissue changes, while the mice responded with growth of endometriotic tissue.^{31,33}

Studies using mice also found that dioxins act as a disruptor of progesterone action, by blocking the ability of progesterone to prevent ectopic human tissue lesions in mice and by altering the expression of progesterone receptors during gestational development.^{33,59} Further, dioxin can disrupt ovarian synthesis of progesterone and inhibit the steroid regulation of endometrial matrix metalloproteinase (MMP) expression, specifically TGF-B².^{33,34} Progesterone-induced expression of TGF-B² is also critical to maintain an appropriate endometrial environment for pregnancy.³³ Primate studies indicate that TCDD exposure increases spontaneous abortion,³⁶ a uterine event that may be linked to endometriosis.³⁵ Recent work demonstrates that dioxin exposure of human endometrial cells results in reduced expression of progesterone receptor-B and increased MMP expression similar to endometrial tissues from women with endometriosis.³⁷ Progesterone can prevent or minimize endometriosis whereas MMP expression is critical to the establishment of endometrial lesions.³³ Thus, alterations in the ability of endometrium to respond to progesterone and the aberrant expression of MMPs induced by dioxins could mediate the establishment of endometrial lesions.

In addition, a 2001 study of the monkey colony demonstrated both elevated-serum TCDD and elevated serum triglycerides in the monkeys exposed to dioxin.³⁸

What Are PCBs?

PCBs are known to modulate or disrupt the activity of certain steroid and sex hormones, including estradiol, vitamin A (retinoic acid), and thyroid hormones.^{41, 42}

Polychlorinated biphenyls (PCBs) are mixtures of up to 209 individual chlorinated compounds.³⁹ Because they do not burn easily and are good insulators, PCBs appeared in 1929 as coolants and lubricants in transformers, capacitors, and other electrical equipment, rather than occurring in nature (or being produced accidentally, as in the case of dioxins).³⁹ The United States banned the manufacture of PCBs in 1977, but they are still found in the environment, and we need to identify an appropriate means of disposing of or destroying them.

As in the case of dioxins, PCBs do not break down easily in the environment; they are complex chlorinated chemicals, and they bioaccumulate and biomagnify in the food chain. Rachel Carson helped expose the health effects of PCBs in her published observations of birds that revealed thinning eggshells and other reproductive problems.⁴⁰ The list of health problems linked to PCBs mirrors that of dioxins. PCBs are known to modulate or disrupt the activity of certain steroid and sex hormones, including estradiol, vitamin A (retinoic acid), and thyroid hormones.^{41,42} The estrogenic activity of certain PCBs has also been observed in animal studies.⁴³

PCBs and endometriosis

Similar to the general human population and wildlife, TCDD-treated and control animals were exposed to a mixture of PCBs via their diet or other environmental sources.³⁸ Studies have shown that

the same toxic, dioxin-like PCBs found in TCDD-exposed animals with endometriosis are present in wildlife and humans worldwide.⁴⁴

Studies have also documented development of endometriosis and increased severity in rhesus monkeys following exposure to PCBs^{45,46} and certain types of radiation.^{46,47,48} A recent analysis of the original monkey colony exposed to dioxins revealed a surprising finding. The monkey chow that the group of exposed animals consumed was contaminated with TCDD, as part of the experiment; however, the monkey chow itself was contaminated, inadvertently, with PCBs, likely as a component of the fish meal in the chow.³⁸ This is similar to fish that humans consume, which often contain PCBs. Thus, the animals in both the control group and the study group were exposed to PCBs unintentionally (PCB levels were 1,961 PPQ—parts per quadrillion—exposed group; 147 PPQ unexposed group), and this is similar to human populations.^{38,49,50}

Changes in immune status of dioxin-treated animals correlated with elevated serum concentrations of dioxin (TCDD) and certain PCBs.³⁸ The animals with high serum levels of certain PCBs also had more endometriosis and the severity of the disease correlated with the serum level of certain PCBs.³⁸ These findings suggest that PCB exposure may be involved in the pathogenesis of endometriosis in the rhesus monkeys, and increased serum TEQ may play a role in the pathogenesis of endometriosis.³⁸

These findings suggest a relationship between exposure to dioxins and PCBs, severe endometriosis, and altered immune responses.^{51, 60} Early small hospital-based studies on exposure to dioxins and endometriosis in human populations were inconclusive. However, recent work has shown that serum levels of dioxins are increased in women with peritoneal endometriosis and deep endometriotic lesions compared to fertile women without disease.⁵² Moreover, increased serum levels of dioxin-like PCB congeners, combined with elevated levels of non-dioxin-like PCBs, were detected in Italian women with endometriosis.⁵³ Thus, recent human studies indicate that environmental dioxins, including PCBs, play a role in the pathophysiology of endometriosis. The accumulated evidence discussed here supports the hypothesis that “exposure to dioxins (particularly TCDD) and certain PCBs promotes endometriosis via stimulation of chronic inflammation potentially leading to enhanced estrogen synthesis and disruption of progesterone-dependent remodeling responses that normally limit the development of endometriosis.”^{51,65}

Endometriosis and Cancer

The new data show that women with endometriosis (and their families) have a heightened risk of numerous cancers.

In 1996, a major study revealed that women with endometriosis have a greater risk of developing breast cancer, ovarian cancer, and non-Hodgkin’s lymphoma. The study also showed that endometriosis elevated the overall cancer risk by 20%.⁵⁴ Studies at Harvard raised the specter of increased melanoma as well.⁵⁵

An excellent review of the studies on endometriosis and cancer finds compelling evidence for increased malignant potential in endometriosis, including deadly ovarian cancer arising from endometriomas. Other cancers found to be risks for women with endo are endocrine, kidney, thyroid, brain, breast and colon cancers, and non-Hodgkin’s lymphoma and melanoma.⁶⁶

A study utilizing the Endometriosis Association research registry also confirmed the risk of cancer for women with endometriosis. In addition, increased risk of cancer in the families of women with endometriosis was discovered.^{5,57} The new data show that women with endometriosis and their families have a heightened risk of numerous cancers.⁵⁴⁻⁵⁷ Moreover, the mean age of some of the cancers was

much younger in this population. Mean age of ovarian cancer diagnosis was 34 in women with endometriosis compared to the general population age of 52. Breast cancer in the general population is most often diagnosed in middle-aged and older women. In women with endometriosis, the average age of diagnosis was 39 years.⁵⁷

Endometriosis and autoimmune disorders

Results of a major study by the National Institutes of Health and the Endometriosis Association found that women with endometriosis have significantly higher rates of hypothyroidism, fibromyalgia, chronic fatigue syndrome, autoimmune diseases including multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, and allergies, asthma, and eczema.⁵⁸

The study also found that 40% of women with endometriosis had at least one family member with at least one autoimmune inflammatory disease, 34% had at least one endocrine disease, and 48% had fibromyalgia or chronic fatigue syndrome.⁵⁸ Lupus, MS, hypothyroidism, hyperthyroidism, diabetes, fibromyalgia, and chronic fatigue syndrome were more common among family members if the women with endometriosis also had these additional disorders as compared to those who only had endometriosis.⁵⁸

References

1. U.S. EPA. (1994) Risk characterization of dioxin and related compounds—*Draft Dioxin Reassessment*. Washington D.C., Bureau of National Affairs.
2. Ballweg ML and the Endometriosis Association. (2004) *Endometriosis: The Complete Reference for Taking Charge of Your Health*. Contemporary Books, Inc. Chicago, IL.
3. Koninckx PR, Ide P, Vandenbrouck W, Brosens IA. (1980) New aspects of the pathophysiology of endometriosis and associated infertility. *Journal of Reproductive Medicine*, 24:257-260.
4. Vital and Health Statistics, U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control. (1987) *Hysterectomies in the United States, 1965-1984*. National Center for Health Statistics, Series 13(92).
5. Ballweg ML. (2003) Big picture of endometriosis helps provide guidance on approach to teens: Comparative historical data show endo starting younger, is more severe. *Journal of Pediatric and Adolescent Gynecology*. Supplement, 16(3)S21-26.
6. Herman-Giddens M. (1997) Secondary sexual characteristics and menses in young girls seen in office practice: a study from the pediatric research in office settings network. *Journal of Pediatrics*, 99(4):505-512.
7. Moffat S. (8/30/95) Minorities are more likely to live near toxic sites. *Los Angeles Times*, B1.
8. U.S. EPA. (1985) Health Assessment document for polychlorinated dibenzo-*p*-dioxins. Office of Health and Environmental Assessment, EPA/600-8-84/014f.
9. Thornton J. (1994) *Achieving Zero Dioxin: An Emergency Strategy for Dioxin Elimination*. Greenpeace Report.
10. U.S. Food and Drug Administration Report. (1999). *Tampons, Asbestos, Dioxin, & Toxic Shock Syndrome*.
11. DeVito MJ and Schechter A. (2002) Exposure assessment to dioxins from the use of tampons & diapers. *Environmental Health Perspectives*, 110:23-28.
12. Congresswoman Carolyn Maloney, 14th District, NY. (1/27/2003) Protect women from dioxin and toxic shock syndrome: Representative Maloney introduces Robin Danielson Act, Press Release.
13. Knopper M. (2003) How safe are tampons? Truth is, we just don't know. *St. Paul Pioneer Press*.
14. Nassar S. (2003) Tampon safety. National Center for Policy Research (CPR) for Women and Families. Online article at <http://www.cpr4womenandfamilies.org/tamponsafety.html>.
15. U.S. EPA. (1979) *EPA's final PCB ban rule: over 100 questions & answers to help you meet these requirements*. Washington, D.C.; Office of Toxic Substances TS-799.
16. Pirkle JL, Wolfe WH, and Patterson DG, et al. (1989) Estimates of the half-life of 2,3,7,8-TCDD in Vietnam veterans of Operation Ranch Hand. *Journal of Toxicology and Environmental Health*, 27:165-171.
17. Eskanazi B, Mocarelli P, Warner M, Needham L, Patterson DG Jr., Samuels S, Turner W, Gerthoux PM, Brambilla P. (2004) Relationship of serum TCDD concentrations and age at exposure of female residents of Seveso, Italy. *Environmental Health Perspectives*, 112(1):22-7.

18. DeVito MJ, Birnbaum LS, Farland WH, Gasiewica TA. (1995) Comparisons of estimated human body burdens of dioxinlike chemicals and TCDD body burdens in experimentally exposed animals. *Environmental Health Perspectives*, 103:820-831.
19. Pulim HJ, Koppe JG, Olie K, Van De Slikke JW, Kok JW, Uulsma T, Van Tijn D, and De Vijlder JJM. (1993) Effects of dioxins on thyroid function in newborn babies. *Lancet*, 339:1303.
20. Schechter A. (1991) Dioxin in humans and the environment. Biological basis for risk assessment of dioxins and related compounds. *Banbury Report*, 35:169-214.
21. Whitlock JP. (1990) Genetic and molecular aspects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin action. *Annual Review of Pharmacology*, 30:251-277.
22. Rier SE, Martin DC, Bowman RE, and Becker JL. (1995) Immuno-responsiveness in endometriosis: implications of estrogenic toxicants. *Environmental Health Perspectives*, 103(Suppl 7):151-156.
23. Rier SE, et al. (1993) Endometriosis in rhesus monkeys (*macaca mulatta*) following chronic exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Fundamental and Applied Toxicology*, 21:433-441.
24. Tabibzadeh S. (1994) Cytokines and the hypothalamic-pituitary-ovarian-endometrial axis. *Human Reproduction*, 9:947-967.
25. Rier S and Yeaman G. (1997) *Immune Aspects of Endometriosis: Relevance of Uterine Mucosal Immune System*. Department of Microbiology, Dartmouth Medical School, Lebanon, New Hampshire. Thieme Medical Publishers, Inc., New York, New York.
26. Taylor MJ, et al. (1990) 2,3,7,8-tetrachloro-dibenzo-*p*-dioxin (TCDD) increases the release of tumor necrosis factor- α (TNF) & induces ethoxyresorfin-O-deethylase (EROD) activity in rat Kupffer's cells (KCs). *Toxicologist*, 10:276-282.
27. Clark GC, et al. (1991) Tumor necrosis factor involvement in 2,3,7,8-tetrachlorodibenzo-*p*-dioxin-mediated endotoxin hypersensitivity in C57BL/6j mice congenic at the Ah locus. *Toxicology & Applied Pharmacology*, 111:422-431.
28. Hoglen N, et al. (1992) Effects of xenobiotics on serum tumor necrosis factor (TNF) and interleukin-6 (IL-6) release after LPS in rats. *Toxicologist*, 12:290-297.
29. Jones MK, et al. (1987) Circadian alterations in prolactin, corticosterone, and thyroid hormone levels and down-regulation of prolactin receptor activity by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Toxicology & Applied Pharmacology*, 87:337-352.
30. Safe S. (1991) 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and related compounds as antiestrogens: characterization and mechanism of action. *Pharmacology Toxicology*, 69:400-409.
31. Cummings AM and Metcalf JL. (1995) Effects of estrogen, progesterone, and methoxychlor on surgically induced endometriosis in rats. *Fundamental and Applied Toxicology*, 27:287-290.
32. Osteen KG, et al. (1996) Dioxin (TCDD) can block the protective effect of progesterone in nude mouse model of experimental endometriosis. 52nd Annual Meeting of the American Society for Reproductive Medicine, November 1996, Boston, MA.
33. Bruner-Tran K, Rier S, Eisenberg E, and Osteen K. (1999) The potential role of environmental toxins in the pathophysiology of endometriosis. *Gynecologic & Obstetric Investigation*, Supplement:45-56.
34. Enan E, et al. (1996) 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) modulates function of human luteinizing granulosa cells via cAMP signaling and early reduction of glucose transporting activity. *Reproductive Toxicology*, 10(3):191-198.
35. Damewood M. (1989) The association of endometriosis and repetitive (early) spontaneous abortions. *Seminars in Reproductive Endocrinology*, 7:155-160.
36. Bowman RE, et al. (1989) Chronic dietary intake of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) at 5 or 25 ppt in the monkey: TCDD kinetics and dose-effect estimates of reproductive toxicity. *Chemosphere* 18:243-252.
37. Igarashi TM, et al. (2005) Reduced expression of progesterone receptor-B in the endometrium of women with endometriosis and in cocultures of endometrial cells exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Fertility Sterility* 84(1): 67-74.
38. Rier S, et al. (2001) Serum levels of TCDD and dioxin-like chemicals in rhesus monkeys chronically exposed to dioxin: correlation of increased serum PCB levels with endometriosis. *Toxicological Sciences*, 59(1):147-159.
39. Agency for Toxic Substances and Disease Registry. (2001) ToxFaqs for polychlorinated biphenyls (PCBs). Web site factsheet <http://www.atsdr.cdc.gov/tfacts17.html>.
40. Carson R. (1962) *Silent Spring*. Houghton Mifflin, Cambridge, Massachusetts.
41. Safe SH. (1994) Polychlorinated biphenyls (PCBs): environmental impact, biochemical and toxic responses, and implications for risk assessment. *Critical Review of Toxicology*, 24: 87-149.
42. Whitlock JP. (1994) The aromatic hydrocarbon receptor, dioxin action, and endocrine homeostasis. *Trends in Endocrinological Metabolism*, 5:183-188.
43. Nesaretnam K, et al. (1996) 3,4,3',4'-Tetrachlorobiphenyl acts as an estrogen in vitro and in vivo. *Journal of Molecular Endocrinology*, 10: 923-936.

44. Tanabe S, Kannan N, Subramanian A, Watanabe S, Tatsukawa R. (1987) Highly toxic coplanar PCBs: occurrence, source, persistency and toxic implications to wildlife and humans. *Environmental Pollution*, 47(2):147-163.
45. Campbell JS, et al. (1985) Is simian endometriosis an effect of immunotoxicity? Presented at the Ontario Association of Pathologists 48th Annual Meeting, London, Ontario, Canada.
46. Fanton JW, Golden JG. (1991) Radiation-induced endometriosis in macaca mulatta. *Radiation Research*, 126:141-146.
47. Wood DH, Yochmowitz MG, Salmon YL, Eason RI, Boster RA. (1983) Proton irradiation & endometriosis. *Aviation in Space Environmental Medicine*, 54:718-724.
48. Wood DH. (1991) Long-term mortality and cancer risk in irradiated rhesus monkeys. *Radiation Research*, 126:132-36.
49. Clark G, et al. (1992) Integrated approach for evaluating species and interindividual differences in responsiveness to dioxins and structural analogs. *Environmental Health Perspectives*, 98:125-132.
50. Crook D, et al. (1997) Elevated serum lipoprotein (a) levels in young women with endometriosis. *Metabolic Clinical Experience*, 46:735-739.
51. Rier S and Foster W. (2002) Forum: environmental dioxins and endometriosis. *Toxicological Sciences*, 70:161-170.
52. Heilier JF, Nackers F, Verougstraete V, Tonglet R, Lison D, Donnez J. (2005) Increased dioxin-like compounds in the serum of women with peritoneal endometriosis and deep endometriotic (adenomyotic) nodules. *Fertility Sterility* 84:305-12.
53. Porpora MG, Ingelido AM, di Domenico A, Ferro A, Crobu M, Pallante D, Cardelli M, Cosmi EV, De Felip E. (2006) Increased levels of polychlorobiphenyls in Italian women with endometriosis. *Chemosphere* 63:1361-7.
54. Brinton LA, et al. (1996) Cancer risk after a hospital discharge diagnosis of endometriosis. *American Journal of Obstetrics & Gynecology*, 176(3):572-579.
55. Hornstein MD, et al. (1997) Association between endometriosis, dysplastic nevi and history of melanoma in women of reproductive age. *Human Reproduction*, 12:143-145.
56. Vercellini P, Parazzini F, Bolis G, et al. (1993) Endometriosis and ovarian cancer, *American Journal of Obstetrics and Gynecology* 169(1):181-182.
57. Ballweg, ML and the Endometriosis Association. (2004) *Endometriosis: The Complete Reference for Taking Charge of Your Health*. New York: McGraw-Hill/Contemporary Books.
58. Sinaii N, et al. (2002) High rates of autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome and atopic disease among women with endometriosis: a survey analysis. *Human Reproduction*, 17(10):2715-2724.
59. Nayyar T, Bruner-Tran KL, Piestrzeniewicz-Ulanska D, Osteen, KG. (2007) Developmental exposure of mice to TCDD elicits a similar uterine phenotype in adult animals as observed in women with endometriosis. *Reproductive Toxicology*, 23(3): 326-336.
60. Birnbaum LS, Cummings, AM. (2002) Dioxins and Endometriosis: A Plausible Hypothesis. *Environmental Health Perspectives*, 110(1): 15-21.
61. Bailey MT, Coe CL. (2002) Endometriosis is associated with an altered profile of intestinal microflora in female rhesus monkeys. *Human Reproduction*, 17(7): 1704-1708.
62. Ying-Li Shi, Xue-Zhen Luo, Xiao-Yong Zhu, Da-Jin Li. (2007) Combination of 17 β -estradiol with the environmental pollutant TCDD is involved in pathogenesis of endometriosis via up-regulating the chemokine I-309-CCR8. *Fertility and Sterility*, 88(2): 317-325.
63. Zhao D, Pritts EA, Chao VA, Savouret JF, Taylor RN. (2002) Dioxin stimulates RANTES expression in an in-vitro model of endometriosis. *Molecular Human Reproduction*, 8(9): 849-854.
64. Bulun SE, Zeitoun KM, Kilic G. (2000) Expression of dioxin-related transactivating factors and target genes in human eutopic endometrial and endometriotic tissues. *American Journal of Obstetrics and Gynecology*, 182(4): 767-775.
65. Bruner-Tran KL, Yeaman GR, Crispens MA, Igarashi TM, Osteen KG. (2008) Dioxin may promote inflammation-related development of endometriosis. *Fertility and Sterility*, 89(3): 1287-1298.
66. Nezhat F, Datta S, Hanson V, Pejovic T, Nezhat CH, Nezhat C. (2008) The relationship of endometriosis and ovarian malignancy: a review. *Fertility and Sterility*, 90(5): 1559-1570.