VALLOMBROSA CONSENSUS STATEMENT ON ENVIRONMENTAL CONTAMINANTS AND HUMAN FERTILITY COMPROMISE OCTOBER 2005

NB: Terms in blue underlined font are defined in a Glossary of Terms and Term Usage specific to this document.

Introduction

A recent national survey indicates that 12% of the reproductive age population in the United States, or 7.3 million couples, reports experiencing difficulty conceiving and/or carrying a pregnancy to term. This is precisely termed impaired fecundity, but commonly referred to, as a general experience, as infertility. Proximate causes of infertility vary widely; for example, from impaired sperm quality or reproductive tract abnormalities, to fallopian tube obstruction, hormone/menstrual cycle irregularities and anovulation, to implantation difficulties and recurrent miscarriage. Some seek medical intervention to help them conceive, and the number of people doing so has risen sharply over the last two decades. In 2002, an estimated $2.9 billion was spent on infertility treatments in the United States. Now, some 46,000 (or one in 100) babies born to Americans each year are conceived as a result of the most advanced assisted reproductive technologies (ART).

These increasingly effective medical procedures have helped hundreds of thousands of couples around the world achieve successful pregnancies. They can, however, also be a hardship emotionally and/or financially, and often the financial costs place these interventions beyond the reach of couples who need them.[1] For those who can pursue such assistance, despite its great promise, success is not a given: An estimated one fifth or more of treated couples do not end up with a baby after a course of ART cycles. Too, other medical and/or mental health conditions can be associated with infertility in the couple experiencing it (and research is ongoing as to whether there are increased health risks that attend treatment or conception via ART). In light of all these considerations, a high value should be placed on minimizing preventable causes of infertility as well as on the treatment of it.

Multiple interacting factors are likely to contribute to biological fertility challenges, including age, heredity, lifestyle, underlying disease, reproductive tract infections and nutritional status. Demographers have identified voluntary delays in first pregnancy as a major factor. Yet, data from the US Centers for Disease Control and Prevention show that impaired fecundity over the last two decades appears to have increased in all reproductive age groups, but most sharply in *younger* women (under age 25). These data, together with a growing body of epidemiological literature and many experimental research results showing male and female fertility-related impairment in laboratory animals caused by a wide array of modern chemicals, implicate environmental factors also as possible contributors to human infertility.

Scientific understanding of the relationship between environment and human health is advancing rapidly. It reveals that a larger portion of health problems, including infertility, may be caused by environmental exposures than thought possible even a decade ago. These exposures include but are not limited to occupational sources. For some environmental agents known to have adverse effects in experimental animal studies or wildlife, impacts on human reproductive health are being found as well, and at exposure levels within the range humans commonly experience (termed “environmentally relevant”). If involuntary infertility *is* actually on the rise, and

[1] In the US, only 14 states have any form of mandate requiring health insurers to cover or offer coverage for infertility treatments, and more often than not such coverage is only partial at best.

troubling insights from animal studies accurately predict human impacts, then the personal and societal costs of fertility compromise could become increasingly burdensome and significant shifts in reproductive health and norms at the level of whole populations could occur. This has profound implications for public health and strongly suggests that a more comprehensive, coordinated research agenda must be developed and funded – because adverse effects caused by environmental exposures are, in principal, preventable.

Responding to these concerns, a multidisciplinary group of experts gathered at the Vallombrosa Center, Menlo Park, CA, February 27- March 1, 2005 to assess what is known about the contribution of environmental contaminants, specifically synthetic compounds and heavy metals, to human infertility and associated health conditions. Workshop organizers chose this focus because critical recent discoveries in the field have raised many new, intriguing scientific questions and heightened interest in environmental risk factors within patient organizations and reproductive medicine/science professional societies. This was the first time researchers in reproductive epidemiology, biology, toxicology and clinical medicine convened with representatives of relevant professional societies as well as infertility support, women's health and reproductive advocacy organizations from the United States to review the state of environmental health science as it pertains to infertility.

The purposes of the meeting were:

- To review findings from diverse research disciplines concerning environmental contaminants and the biological basis of compromised fertility, with special attention to critical recent discoveries in related basic sciences;
- To identify conclusions that could be drawn with confidence from existing data;
- To identify critical knowledge gaps and areas of uncertainty;
- To establish key elements of a coherent research agenda to help fill these gaps and resolve uncertainties;
- To consider recommendations for educational initiatives and preventive interventions if and where warranted.

Rapid advances and critical recent discoveries:

- Even very low doses of some biologically active contaminants can alter gene expression important to reproductive function.
- Exposures during fetal development can adversely affect health of the individual in adulthood, including reproductive health.
- Humans are exposed to complex mixtures of chemicals that can interact to cause increased effects.
- People differ in susceptibility to exposures. Not identifying and studying susceptible subgroups can result in failure to detect even very high risk.

Over the course of the meeting, the following core points of consensus were identified, which we offer to help scientists, medical professionals and public health advocates understand, in broad brush, the current state of scientific understanding in the field and to identify important research areas that will be crucial to further advances:

A. Based on existing evidence, we are confident of the following:

1. In the US today, at least 12% of the reproductive age population reports experiencing impaired fecundity. This appears to be a rising trend, most markedly in women under 25 years old.

2. Human biological characteristics relevant to fertility vary geographically and over time. For example, semen quality varies within and between men and geographically among populations. Hypospadias, cryptorchidism and testicular cancer are increasing in some areas but not in others. Other fertility-related diseases, for example endometriosis and polycystic ovarian syndrome (PCOS), are diagnosed more frequently now, which may result from an increase in prevalence, better detection, or both. Current data are inadequate to analyze global trends conclusively.

It is helpful to distinguish between **"proximate" and "ultimate" causes of infertility.** A proximate cause might be reduced sperm quality, hormone imbalances, endometriosis, etc. It is a factor preventing successful conception or pregnancy.

But what causes the proximate cause? Why is sperm quality reduced, for example? An ultimate cause is the factor (or factors) responsible for the proximate cause.

3. Specialists can identify proximate (or apparent) cause or risk factors in the male, female or couple in the majority of infertility cases. Within this "explained" category, however, sometimes ultimate (or underlying) causes and mechanisms are understood, but very often they are not. In up to 10% of cases, absolutely no reason for the infertility can be discovered at all – and in a much higher percentage than that, only minor abnormalities that are not severe enough to account for the infertility are identified. These cases are termed "unexplained." It is biologically plausible that environmental factors could be contributing to (or a component of) ultimate causation of infertility, in both the explained and unexplained case categories.

4. Considerable data from experimental animal and human studies demonstrate adverse effects of cigarette smoke on a spectrum of sensitive reproductive endpoints in both men and women. Cigarette smoke contains thousands of chemicals, some of which are thought to be involved in its impact on reproduction. These compounds are also encountered elsewhere in the environment, and there is no a priori reason to eliminate these exposure pathways from concerns about reproductive health. Effects of other environmental mixtures are likely to be similarly diverse and complex.

Potential effects of exposure to cigarette smoke include menstrual abnormalities; longer time to pregnancy; increased risk of pregnancy loss; earlier menopause; shortened gestation; intrauterine growth restriction; lower IVF success rates. In males, smoking is associated with impotence; subfertility; reduced semen quality and damage to sperm DNA. Sons of mothers who smoke while pregnant have been reported to have lower sperm counts.

5. Considerable experience with the pharmaceutical diethylstilbestrol (DES) clearly demonstrated that prenatal exposure to a synthetic estrogen can adversely affect reproductive physiology and impair fertility later in life, with many endpoints altered. This compound serves as a model for environmental agents that are hormonally active, in other words, endocrine disruptors. Laboratory experiments with DES-exposed animals have repeatedly demonstrated causal effects that are congruent with data on DES offspring, particularly DES daughters. While doses of DES ingested by pregnant women were much greater than those that come from exposure to environmental estrogens, many underlying mechanisms of action appear to be similar.

6. Moreover, environmental contaminant concentrations and/or potency can be amplified because of persistence (biomagnification and bioaccumulation) and because they always occur in mixtures.

7. A wide range of wildlife populations has been shown to be adversely affected by exposure to endocrine-disrupting contaminants. Well-documented effects include: decreased fertility and increased reproductive tract abnormalities in birds, fish, shellfish and mammals; feminization

and demasculinization in male fish, birds, mammals and reptiles; masculinization and defeminization in female fish, birds, mammals and reptiles.

8. Some environmental contaminants at high, occupational exposure levels were shown decades ago to impair human fertility, for example lead and the fumigant dibromochloropropane. These types of exposures, however, are unlikely to explain more than a small fraction of the infertility observed in today's population. More recently, considerable data support the contention that exposure to certain agricultural pesticides at moderate or environmentally relevant exposure levels are associated with adverse reproductive outcomes in men and women working on or living near farms (male subfertility and sperm damage; menstrual alterations, increased time to pregnancy and spontaneous miscarriage rates).

9. Recent research with animals has demonstrated effects on specific aspects of reproductive system development at very low levels of exposure to environmental contaminants (levels within ranges experienced by the general public). This is a finding that may ultimately alter how human safety thresholds are established. In animal and cell culture experiments using these low-dose exposure levels, some contaminants, for example bisphenol A and dioxin**,** have been shown to interfere with cellular signaling pathways that are important to fertility and reproduction. Proposed mechanisms through which such chemicals may act include perturbation of nuclear hormone signaling, inappropriate activation or inactivation of transcription factors and alterations in hormone metabolism. For some contaminants, nonmonotonic dose-response curves have been observed when responses are examined across a wide range of exposure levels.

10. Very few relevant data from epidemiological studies are available to investigate the possible associations suggested by these studies between low-level environmental exposures and reproductive health. Much more work in this area must be done given the import if animal data on low-dose effects translate to humans.

11. Genetic signaling mechanisms are highly similar across vertebrate classes, particularly with respect to the structure of key signaling molecules such as steroid hormones and their receptors. Animal models of reproductive toxicity thus offer useful guidance for identifying potential reproductive toxicants in humans. For some compounds, especially DES, there has been remarkable concordance of responses between humans and other vertebrates. A similar pattern is emerging in studies of phthalates. Although differences do exist, consistency of impact across multiple species (especially if the species are from diverse vertebrate classes, e.g. birds and mammals and fish) increases the utility of animal data for identifying human reproductive toxicants.

12. Single contaminants can affect multiple endpoints in more than one tissue through alterations in the expression of multiple genes affecting multiple pathways. Some contaminants have been shown to alter the expression of hundreds of genes, and effects can vary with timing and dose. Different contaminants can affect the same physiological endpoint by acting on the same signaling pathway.

13. Genetic variation, or DNA polymorphisms, within populations (humans, wildlife and laboratory animals) can result in greater sensitivity to specific contaminants in some individuals. While such variation/sensitivity has been linked to increased risk of specific problems such as, for example, bladder cancer and fetal alcohol syndrome, it has yet to be discovered whether there are genetic polymorphisms that affect response to environmental toxicants *and* cause or contribute to infertility.

14. Recent measurements of contaminants in people show that humans are exposed, starting at conception, to at least hundreds of chemicals simultaneously – and some at levels within ranges known individually (chemical by chemical) in cell culture and/or animal studies to affect physiological processes relevant to reproduction.

15. The effects of a single chemical exposure have been shown in laboratory studies to differ from the effects of the same chemical in a mixture. Experiments with single chemicals can significantly underestimate effects of the same chemical in mixtures.

16. Exposures during different stages of life (pre- and periconceptional, fetal, perinatal, peripubertal and adult) have different impacts, because developmental processes create discreet windows of vulnerability for specific effects. The consequences of exposure can manifest on different time scales, some involving long latency. For example, prenatal exposures can cause abnormalities at birth or later that have impacts on adult reproductive function (e.g. as shown with DES). The abnormalities may involve structural or functional alterations, or enhanced sensitivity to subsequent endogenous or exogenous exposures.

17. To date few if any epidemiological studies have successfully incorporated the full complement of these considerations (assessing mixtures, life stage of exposure, the possibility of differential individual genetic susceptibility, etc.) into study design. Epidemiological research that does not factor in these biological considerations will be more likely to conclude erroneously that a study is "negative" and less likely to confirm adverse impacts. Facing these limitations, when epidemiological studies do report positive associations, they should be taken seriously.

18. New scientific methods and tools can and should be developed to further scientific understanding of environmental contributions to human infertility and identify opportunities for preventive interventions. *However, a current lack of adequate research funding in the field is a significant impediment.*

B. We consider the following to be likely but requiring confirmation:

1. It is likely that gene-environment interactions are involved in the etiology of many reproductive problems including impaired sperm quality; PCOS; endometriosis; uterine fibroids; premature puberty, ovarian failure and menopause; and reproductive cancers. Further, it is possible that environmental (i.e. low-level ambient) exposures having the biggest impact are those that occur before conception, in utero and neonatally.

2. A cluster of abnormalities of the male reproductive tract is associated in what is termed "testicular dysgenesis syndrome" (TDS), which is hypothesized to originate from a common causal pathway of developmental errors in the fetal testis. TDS can produce a range of outcomes including cryptorchidism and hypospadias at birth, and reduced sperm quality and testicular cancer in adulthood. Semen quality in specific populations has declined (though with no geographic uniformity), and several recent epidemiological studies suggest this may be related to environmental agents. The mechanisms have not been established.

3. It is likely that environmental endocrine disruptors contribute to some manifestations of TDS in humans. In the etiology of TDS, some evidence points to interference with testosterone metabolism mediated by disruption of genetic signaling. Given the well-known, multiple effects of DES on male and female reproductive tract development, it is likely that a syndrome

analogous to TDS involving interference with estrogen signaling by environmental chemicals will be identified.

4. It is likely that a broad spectrum of women's reproductive health endpoints is affected by environmental agents including heavy metals, polychlorinated biphenyls (PCBs) and other hormonally active chemicals. Attributing risk of adverse reproductive effects from these exposures is challenging, but several female-factor secular trends in some populations lend biological plausibility to such an association and support the need for further research. For example, *increases* in the incidence of reproductive cancers may reflect non-hereditary genetic factors, lifestyle and/or environmental factors or exposures. Age at onset and progression of puberty have been reported to be decreasing over time in several developed countries, suggesting environmental etiology inclusive of lifestyle and diet. Similarly, as prevalence of endometriosis is reported to be increasing, earlier ages at diagnosis are also noted. While greater access to medical care may account for some of these temporal patterns, accumulating evidence suggests an etiologic role for environmental contaminants.

5. Current data contradict the assumption that "weak" environmental estrogens are not a concern because of their low estrogenic potential compared to the endogenous estrogen, estradiol. Studies of mixtures in cell cultures and animals indicate that multiple "weak" estrogens can combine to have effects even when present at levels at which singly they would have no impact. Additionally, some "weak" estrogens affect cellular signaling through recently discovered cell membrane receptors as well as through "traditional" nuclear hormone receptor mediated pathways. In the former case, "weak" estrogens like bisphenol A can be equally as powerful as estradiol at provoking cellular responses.

Contaminants of Concern?

Contaminants implicated by research as having effects on fertility/reproductive health fall into a wide range of chemical types. Some are persistent; some are not. Common sources of exposure include a vast array of consumer products (e.g. beauty, personal and home care, as well as home furnishing and decorating products), food and water, hobbies, arts and crafts. Exposures can happen at home, work, school, play – and in utero. Certain occupations put employees at greater risk of toxic chemical exposures, for instance work that involves solvents (e.g. nail salons, laboratory work, mechanics), pesticides (agricultural work, applicators), plastics manufacturing/dismantling, welding, painting, etc. Exposure pathways are multiple and vary from compound to compound. Common routes are through air, water (drinking and bathing), food, soil and household dust - via ingestion, inhalation and/or absorption through the skin.

Examples of chemicals and heavy metals of concern:

Persistent

Dioxins/furans, polychlorinated biphenyls, polybrominated diphenyl ethers, organochlorine pesticides, lead, perfluorinated compounds.

Not persistent

Triazine herbicides (e.g., atrazine), organophosphate pesticides, solvents including toluene, xylene, styrene and perchloroethylene, methyl mercury, phthalates, bisphenol A, tobacco smoke.

C. Research on a wide array of fertility-related endpoints suggests several broad themes which we believe should be pursued in future scientific investigations:

1. Information about rates of infertility/subfecundity and specific contributing health conditions in the *general population* is very limited. For most fertility/fecundity-related endpoints, we have no population data and must rely on women, men or couples seeking medical treatment. These data are unlikely to be representative of the total population of couples of reproductive age. For this reason, the magnitude of fertility/fecundity impairments has not been fully described and

quantified. This poses a challenge to scientists when attempting to assess trends or environmental influences on human reproductive health. Standardizing definitions, identifying consistent endpoints that can be compared across studies and better public health tracking of fertility/fecundity-related endpoints would strengthen the investigation of environmental associations with reproductive health compromise. More research into geographic variations and factors contributing to differences among populations would also be highly useful.

2. Highly reproducible effects in animal studies indicate that today's framework for evaluating environmental chemical risks to reproductive health is inadequate. Study designs should explicitly incorporate the complex causal framework that has emerged from animal research, including long latencies (of effect following preconceptional, in utero, neonatal and peripubertal exposures) and interactions among multiple factors (mixtures of contaminants; gene-contaminant interactions; pharmaceuticals; subpopulations varying in genetic susceptibility; nutrition and lifestyle; complex dose-response relationships). Study designs must also be broadened to incorporate the possibility of multigenerational, epigenetic transmission of effects; consider a multiplicity of causal pathways and endpoints; and examine impacts on population-level endpoints such as sex ratio.

3. Research on wildlife populations and mechanistic studies in animals and cell cultures have proven invaluable in identifying new categories of risk and elucidating the biological mechanisms linking cause to effect. A vigorous research agenda using these approaches should be continued and expanded. These animal studies would ideally involve multidisciplinary approaches that develop biomarkers of exposure and disease in animal models and translate them for use in epidemiological and clinical studies. They should assess syndromes of impacts in addition to single effects. Human epidemiological data identifying fertility impairments can help guide the animal research.

4. Some human data are consistent with the reproductive effects observed in animals, but epidemiological studies confirming human impacts are rarely definitive, due in part to the multiplicity of variables in human studies. Therefore, a high priority should be placed on expanding relevant animal data and improving the sensitivity of animal test protocols, as well as developing better study protocols for testing hypotheses in humans.

5. Prospective studies of exposures, outcomes and covariates, with high degrees of public participation and cooperation, are likely to be most helpful. For example, the National Children's Study plans to include the recruitment of couples prior to conception to explore fecundity-related impairments in relation to a host of environmental factors including chemicals. This landmark study could also include newly proposed developmental landmarks indicative of endocrine function in infants and be extended to evaluate fertility/fecundity in adulthood, as well as population level outcomes (such as changes in sex ratios, twinning and birth rates).

6. Factors contributing to differential vulnerability to environmental exposures are diverse and include age; gender; genetic and epigenetic variation; nutritional status and obesity; infections; lifestyle behaviors; pharmaceutical use; occupation; socioeconomic and racial disparities; and physical proximity to certain industries or industrial accidents. All of these factors need to be evaluated to help identify biologically sensitive and otherwise vulnerable subgroups. More systematic attention to these subgroups is likely to improve sensitivity and accuracy of epidemiological research designed to assess risks associated with exposures.

7. Developing tools of toxicogenomics, proteomics, metabolomics and the study of genetic variation (toxicogenetics) should be integrated with biomonitoring in epidemiological studies. These tools need to be developed to the point of defining specific biomarkers of susceptibility, exposure and disease. Specific markers for ovarian and testicular responses need to be developed. Increased sensitivity, availability and affordability of assays for measuring contamination levels in people would enhance research in epidemiology and clinical settings.

8. Testicular dysgenesis syndrome is emerging as a useful construct for organizing hypotheses about some aspects of male reproductive health, including infertility. Human patterns appear to be consistent with animal data, and information about impacts of contaminants on gene expression thought to be important for male reproductive development is providing insights into molecular mechanisms. We need a comprehensive national program, coordinated with efforts underway elsewhere in the world, in order to fully evaluate the TDS hypothesis – including TDS prevalence and etiology. This research program should combine epidemiological and clinical perspectives with in vivo and in vitro experimental research that targets mechanisms.

9. Research on both prevalence trends in and environmental causes of female infertility factors is of equally high priority and must be encouraged. Premature ovarian failure (POF); premature menopause; thyroid disruption; autoimmune disorders; menstrual cycle defects; PCOS; uterine fibroids; endometriosis; meiotic aneuploidy; and repeat pregnancy loss are examples of proximate explanations for female factor infertility that call for specific examination to develop understanding of potential environmental etiologic links.

10. A coherent environmental reproductive health research strategy should include a pointed emphasis on high priority compounds, i.e. those that are under-investigated; those that are bioactive at low doses; and those for which potential for exposure is widespread due to persistence or continuous use.

High priority compounds include (but are not limited to):

- current-use pesticides
- phthalates
- bisphenol A
- polybrominated flame retardants (PBDEs)
- perfluorinated compounds(PFCs)
- octyl/nonylphenols

Conclusion

The scientific evidence we have reviewed indicates that while environmental contaminants are unlikely to be the sole etiologic factor underlying human infertility, some exposures cause adverse reproductive health outcomes that contribute to infertility. What proportion of infertility today is environmentally induced is a question of profound human, scientific and public policy significance. Existing animal and human data suggest that a greater proportion is environmentally caused than has yet been generally realized or can be demonstrated with scientific certainty.

Nothing is more fundamental to the human prospect than the ability to reproduce. Uncertain as the science on environmental causes of infertility is, it is sufficient to raise troubling questions about the future of human reproductive health, and serious debate about how to communicate the information accumulated to date to physicians, patients and the public. This amply justifies an accelerated research program built around interdisciplinary coordination and collaboration to resolve important uncertainties that currently prevail, particularly around issues involving low-level developmental exposures. A coherent, enhanced research agenda will help identify new strategies to prevent infertility, through actions that individuals can take as well as those that public health/regulatory agencies can pursue. As these investigations progress, it will be

increasingly important to engage physicians, other health professionals, patients and the public in formalized educational efforts that delineate and encourage opportunities for prevention that are elucidated by the research.

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The listing of organizational affiliation for individual signatories is for identification purposes only and does not imply organizational endorsement of this statement.

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Glossary of Terms and Term Usage Specific to This Statement

Aneuploidy – The loss or gain of chromosomes in a cell due to errors in cell division, e.g. three number 21 chromosomes (or trisomy 21, also called Down syndrome) is a form of aneuploidy.

Assisted reproductive technologies – The handling of eggs and sperm outside the body for the purpose of conception. The acronym ART is sometimes used imprecisely to refer to the whole range of infertility treatments, including both "lower tech" therapies, such as the use of ovulation induction drugs and intrauterine insemination, and "high tech" therapies, namely in vitro fertilization, gamete intrafallopian transfer, and zygote intrafallopian transfer. However, the American Society of Reproductive Medicine, the Society of Assisted Reproductive Technology and the US Centers for Disease Control and Prevention (for the purposes of their data collection) define ART as including only the "high tech" therapies. Therefore, the CDC figure for the number of babies born annually as a result of ART (46,000) excludes the number of children conceived and born as a result of lower tech therapies.

Bioaccumulation – Process whereby contaminants taken up from the surrounding environment (air, food, water) are retained and concentrate in tissues at a rate faster than they can be broken down and excreted. With bioaccumulation, tissue levels of a contaminant become greater than surrounding environmental levels.

Biomagnification – Process whereby the concentration of contaminants increases up the food chain due to larger organisms ingesting smaller organisms containing contaminants. Humans and other predatory organisms accumulate the highest concentrations of contaminants.

Biomarker – A biological substance found in body fluids (blood, urine, breast milk) or tissues (fat) that can be measured and is associated with exposure to a contaminant. Biomarkers can help to monitor exposure to contaminants and may help to characterize individual susceptibilities to exposure. A **biomarker of exposure** is a measure of either the contaminant or a metabolite occurring shortly after exposure. A **biomarker of effect** is a persistent genetic change caused by a contaminant exposure that can be measured by changes in DNA or chromosome structures (e.g. DNA mutations). Biomarkers of effect are not necessarily specific to contaminant exposure. A **biomarker of susceptibility** is a gene or expression of a gene (polymorphisms) that renders an individual more vulnerable to the adverse effects of contaminant exposure. For example, due to differences in enzymes some individuals may not be able to detoxify a contaminant as efficiently as others resulting in higher levels of exposure and greater toxicity.

Biomonitoring – The assessment of exposure to contaminants by measuring biomarkers of exposure in body tissues or fluids (e.g. blood, urine, breast milk, amniotic fluid, hair, adipose tissue, bone). Can be used to monitor not only exposures in populations but also changes in levels of contaminants over time.

Bisphenol A – A common chemical compound that forms the building block of polycarbonate plastics and epoxy resins. Bisphenol A is used in polycarbonate plastic in food containers, water bottles, baby bottles, CD cases, eye glass lenses, the lining of food cans, and as a dental sealant. It binds with nuclear and extracellular estrogen receptors.

Cell membrane receptors – A protein found on the surface of a cell that binds only specific chemical messengers, such as another protein or hormone. Binding of the specific chemical to the cell membrane receptor triggers processes inside of the cell, such as ion flux or enzyme activation.

Cellular signaling – Process whereby one cell communicates with nearby cells to regulate and coordinate function. Communication can occur through direct cell-to-cell contact or through secretion of biologically active substances that inhibit or stimulate cell function. Contaminant exposure can affect cellular signaling by stimulating or inhibiting these biological signals.

Cryptorchidism – Birth defect in newborn males in which one or both of the testicles has not descended into the scrotum. Cryptorchidism is a risk factor for testicular cancer later in life.

Diethylstilbesterol (DES) – Synthetic estrogen given as a feed additive to livestock and prescribed for pregnant women from 1947-1971 to prevent miscarriage (experimental use began in 1941). DES has been shown to interfere with normal development of the reproductive tract resulting in fertility challenge in the sons and daughters of women who took DES during pregnancy. DES daughters also are at risk for a rare form of vaginal cancer.

Dioxins – A class of hundreds of related persistent chemicals, some of which are known to be highly toxic, that result from industrial combustion/incineration processes; burning of household trash or fuels such as wood, coal and oil; chlorine bleaching of pulp/paper; and some types of chemical manufacturing. Cigarette smoke also contains dioxins.

Endocrine disruptors – Environmental compounds that interfere with the normal function of endogenous hormones. Endocrine disruptors can stimulate or block the actions of hormones, or can interfere with their metabolism. Endocrine disruptors continue to be discovered but have been recognized to include a diverse range of chemicals including pesticides, plasticizers, flame retardants, industrial byproducts, pharmaceuticals and plant-derived compounds.

Endogenous – Of or relating to a substance produced within the body, or a naturally occurring chemical. For example, estrogens produced by the ovary are endogenous hormones.

Endometriosis – A chronic condition affecting 5.5 million US women and girls in which the tissue lining of the uterus (endometrium) grows in abnormal locations outside the uterus, such as on the fallopian tubes, ovaries, and in the abdominal/pelvic cavity. Endometriosis causes internal bleeding and thus pain, inflammation and scarring, and is often associated with infertility.

Endpoints – In a scientific study, the outcome that is being measured. This could be a biomarker, toxic effect, disease outcome, or other measure anticipated to differ between exposed and unexposed populations.

Environmental agents – Includes synthetic chemicals, heavy metals (such as lead, mercury, cadmium), and naturally occurring compounds such as plant-derived estrogens. For the purposes of the Vallombrosa Workshop and this document, for the most part focus was limited to those agents considered synthetic **contaminants** in the natural environment. The phrase "**environmental factors"** generally refers to a broader range of possible environmental influences inclusive of alcohol, pharmaceutical use, stress, etc. Contaminants that have been identified as having toxic effects on reproductive physiology, function or health are called **reproductive toxicants**.

Epidemiology – The study of the distribution and determinants of disease (and health-related) states for a human population or sample defined in time and space. Determinants of disease may include sociodemographic, geographic, behavioral, biomedical, or other environmental factors and can be evaluated in the context of genetic factors.

Epigenetic – Refers to DNA modifications that do not involve changes in the sequence of DNA (genotype). Epigenetic changes can affect gene expression (phenotype) and can be transmitted from one generation to the next.

Estradiol – The most potent and biologically active of the estrogens produced by the ovary, it is responsible for many biological functions in the female, including breast development and development of the uterine lining during the first half of the menstrual cycle. Estradiol also can be produced by fat cells in both men and women and can interfere with fertility in cases of obesity.

Exogenous – Of or relating to a substance produced outside of the body, or a synthetic chemical (e.g. estrogens in oral contraceptives are exogenous hormones).

Fecundity – The biologic capacity of men and women for reproduction.

Genetic signaling – Process whereby an endogenous or exogenous substance stimulates a cascade of events inside of a cell to ultimately regulate gene expression. The substance could either inhibit or stimulate gene expression through a cellular signaling pathway.

Hypospadias – Birth defect where the urinary opening (urethra) is found not at the normal location at the tip of the penis but instead on the underside of the penis. In severe cases, the urethral opening may be at the base of the penis or below the scrotum.

Infertility – Definitions and measures of infertility can vary widely, but it is typically diagnosed when a couple is unable to conceive after six months or one year of regular unprotected intercourse. Often the term is used more broadly than in its strict diagnostic sense, i.e. commensurately with **impaired or sub-fecundity,** to describe and encompass any of the range of biological challenges people may encounter in attempting to conceive and/or carry a pregnancy (including conception delay, inability to conceive, pregnancy loss or stillbirth). **Primary infertility** is

infertility in individuals who have never had children. **Secondary infertility** is that experienced after already having given birth to a child or children. **Fertility**, in the precise sense, refers to the ability of women to give birth to a live born infant and for men to be able to father a pregnancy resulting in a live birth. ***About prevalence figures:*** The principle source of infertility prevalence data in the US, the periodic National Survey of Family Growth conducted by the National Center for Health Statistics at US CDC, defines infertility as a duration of greater than 12 months exposed to the possibility of becoming pregnant, but not becoming pregnant. For this measure, the NSFG surveys only married women of reproductive age and reports a 2002 figure of 7.4%. Implicit in this measure is the desire for conception; thus those using contraception and/or not trying to conceive are not reflected. The NSFG also surveys all female respondents of reproductive age (married or not) who are not surgically sterile concerning doctor-diagnosed and self-reported **impaired fecundity**, and indicates that as of 2002 11.9% of US women aged 15-44 report impaired fecundity, compared to 10.2% in 1995 and 8.4% in 1988. Because definitions/measures of infertility vary, there is a wide range of other prevalence estimates. In a study of older women that used five definitions of the word, the age-adjusted prevalence of a history of infertility ranged from 6.1% (when the women reported a physician diagnosis) to 32.6% (unprotected intercourse for 12 months ever, based on a life-time calendar of pregnancy attempts).

Metabolomics – Metabolites are small molecules produced by biochemical processes in cells that build up and/or breakdown substances. Metabolomics, also called metabolic profiling, is the study of metabolites produced by a cell and can reveal much about the physiological state of a cell in response to a chemical exposure.

Mixtures – In this context, concerns the effects of two or more contaminants so that the outcome of exposure is different from their separate effects. The interaction could be additive (a sum of individual effects), subtractive (one substance is stimulatory and another inhibitory), or multiplicative (the effect is greater than the sum of individual effects).

National Children's Study – Led by a consortium of US government agencies (http://nationalchildrensstudy.gov), this study aims to examine prospectively the effects of environmental factors on the health and development of more than 100,000 children from before birth to age 21.

Nonmonotonic dose-response curve – A traditional dose-response curve in toxicology assumes that the response to exposure will increase with increasing dose. This is known as a monotonic curve, i.e. one in which the slope of the dose-response curve does not change from positive to negative or vice versa. In a nonmonotonic dose-response curve, the slope of the dose-response curve changes sign as the level of exposure increases. Some NMDR curves are shaped like a U, others are shaped like an inverted U. NMDR curves are important from a public health perspective because in dose-response curves that are nonmonotonic, low dose effects cannot be predicted from high dose testing. The traditional assumption that higher doses cause greater harm ("the dose makes the poison") is used in standard risk assessment studies to identify the level of a chemical exposure beneath which contamination should cause no effect. This old assumption may be true for many chemicals and for many classic health effects, but it can be misleading for exposures that have a nonmonotonic dose-response curve.

Nuclear hormone signaling – A type of genetic signaling whereby a hormone (estrogen or thyroid hormone, e.g.) binds to its receptor in the nuclear membrane inside a cell and triggers expression of genes associated with the hormone. Endocrine disruptors can interfere with normal hormone signaling to either stimulate or inhibit normal hormone action.

Octyl/nonyl phenols – Chemicals that belong to a broader class of compounds known as alkylphenol ethoxylates (APEs). APEs are high-volume chemicals that have been used for more than 40 years as detergents, emulsifiers, and wetting and dispersing agents. Some uses include: as ingredients in spermicides, cosmetics and detergents; and as inert ingredients in pesticides. Some are endocrine disruptors. Several are noted contaminants in aquatic environments.

Perfluorinated compounds (PFCs) – Persistent, bioaccumulative chemicals found in a wide array of products including stain-resistant coatings for carpets and clothing (Gore-Tex), non-stick cookware (Teflon), and insecticides. Widespread contamination of human tissues has been documented, with some of the highest levels found in US populations.

Persistence – Refers to the stability of a contaminant in the environment. Persistent contaminants are characterized by their ability to resist natural degradation so that they build up in the environment with time. Persistent contaminants often are globally transported on currents of wind or water.

Phthalates – Chemicals added to personal care products to enhance penetration and hold scent/color, and as plasticizers in rigid plastics such as PVC to create flexibility. Phthalates are found in numerous and diverse consumer products including, e.g. vinyl flooring, plastic shower curtains, cosmetics and fragrances, shampoos and lotions, toys, pharmaceutical and herbal pill coatings - and in hospital equipment including IV bags and tubing.

Polybrominated diphenyl ethers (PBDEs) – Persistent, bioaccumulative chemicals added to electronics, upholstery foam, textiles and numerous other materials to make them more flame resistant. PBDEs have a chemical structure very similar to PCBs and have been rapidly accumulating in wildlife and human tissues.

Polychlorinated biphenyls (PCBs) – Persistent, bioaccumulative compounds banned in the US in the late 1970s, although widespread contamination still exists. PCBs were used in hundreds of commercial and industrial applications, including as lubricants, plasticizers, insulators for electrical applications, caulking and paint.

Polycystic ovarian syndrome (PCOS) – A medical condition in which the ovaries produce an excess of male hormones (androgens), develop many small cysts and do not release an egg on a monthly basis. This condition affects 5-10% of women of reproductive age and is a leading cause of infertility. Symptoms include irregular and heavy periods, excessive hair growth, acne and obesity.

Polymorphisms – Variations in DNA sequence (genes) found in a large portion of the population. Polymorphisms may or may not render an individual more susceptible to the toxicity of a contaminant exposure or be linked to a specific form or disease.

Premature ovarian failure (POF) – Occurs in 1- 4% of US females, and is characterized by depletion or dysfunction of a woman's eggs – or ovarian function – prematurely, before the age of 40. In extreme case, POF can occur as early as the teen years.

Proteomics – The study of the structure and function of proteins that are produced by genes inside of a cell and the ways these proteins interact with one another inside of the cell. Exposure to contaminants may affect protein expression and can be studied as a biomarker of exposure.

Transcription factors – A protein that binds to DNA and regulates gene expression.

Toxicogenomics – The study of how genes/gene expression changes in response to exposure to a toxic substance.