Response to Senators Inhofe and Vitter questions following Tracey J. Woodruff's Testimony on February 4, 2010

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1. In your testimony you state that woman are experiencing difficulties in conception and maintaining pregnancy, which you seem to infer is at least partially attributable to the presence of chemicals detected in the body. Was this conclusion based on information you received from physicians or another objective source?

Difficulty in conceiving and maintaining pregnancy can be influenced by either difficulty in achieving conception or difficulty in maintaining a pregnancy. Difficulty in achieving conception includes inability to get pregnant, increased time to pregnancy; difficulty in maintaining pregnancy includes pregnancy loss, such as through spontaneous abortion. Both difficulty in achieving conception and difficulty in maintaining pregnancy have been described in the peer reviewed literature (Mendola et al. 2008; Crain et al. 2008). Difficulty in conceiving can be attributable to overt abnormalities in the reproductive tract, including misshaped or other anatomy abnormalities of the uterus, the oviductal anatomy or cervical anatomy, and endometriosis, which comes from the clinical literature (Crain et al. 2008). For example, prenatal exposure to diethylstilbestrol (DES), an estrogenic compound, is known to increase the risk of abnormalities of the female reproductive tract, including T-shaped uterus, abnormal oviductal anatomy and function, and abnormal cervical anatomy as reported in scientific reviews published in the peer review literature (Diamanti-Kandarakis et al. 2009). Pesticides and persistent pollutants, such as PCBs, DDT, and dioxins, can alter hormone function in women which can increase the risk of adverse reproductive effects in women, which has been identified from scientific reviews published in the peer reviewed scientific literature (Mendola et al. 2008; Diamanti-Kandarakis et al. 2009).

Reported difficulty in conceiving can also be due to male reproductive problems, in particular poor quality or inadequate semen (Hauser and Sokol 2008). Peer reviewed scientific studies in humans have evaluated the relationship between semen quality and several different types of environmental chemicals including certain phthalates, PCBs, dioxins, and nonpersistent pesticides. Recent reviews published in the peer reviewed literature report that all these chemicals have been shown to be associated with poor semen quality or low semen quality in one or more studies. In particular, epidemiological evidence supports the finding that increasing levels of PCBs are associated with a decrease in semen quality, specifically reduced sperm motility (Diamanti-Kandarakis et al. 2009; Hauser and Sokol 2008). PCBs are measured ubiquitously in the US population (Centers for Disease Control and Prevention 2008). The Endocrine Society, the world's oldest, largest, and most active organization devoted to research on hormones and the clinical practice of endocrinology with 14,000 members from over 100 countries representing clinicians,

scientists, industry and allied health fields, published a peer reviewed scientific statement in 2009 that stated "The evidence for adverse reproductive outcomes (infertility, cancers, malformations) from exposure to endocrine disrupting chemicals is strong, and there is mounting evidence for effects on other endocrine systems, including thyroid, neuroendocrine, obesity and metabolism, and insulin and glucose homeostasis" (Diamanti-Kandarakis et al. 2009).

There is a certain percentage of the occurrence for difficulty in conception and maintaining pregnancy for which there is no known cause. A review of the science and the scientific statement published by The Endocrine Society, stated that for female reproductive disorders that "whereas few are polygenic inherited traits and some are due to infections, the pathogenesis of the vast majority of female reproductive disorders is not well understood" (Diamanti-Kandarakis et al. 2009). We do not know the extent to which environmental chemicals are contributing to the portion of disease of unknown etiology, largely because most chemicals in commerce have not been adequately tested for reproductive and developmental health impacts. The evidence that links difficulty in fertility and fecundity to environmental contaminants comes from studies on human and non-human systems. We know three critical pieces of information, namely: (1) studies such as those cited above are part of a growing body of peer-reviewed studies that document an association between exposure to environmental contaminants and adverse reproductive health outcomes, with the strong evidence currently for those chemicals that interrupt the endocrine system; (2) disrupting the endocrine system can adversely impact reproductive health which is dependent on proper hormone function; and (3) the U.S. population incurs multiple ubiquitous exposure to endocrine disrupting and other toxic chemicals (Diamanti-Kandarakis et al. 2009). These three pieces of evidence do not prove that environmental contaminants cause these adverse impacts, but they do provide a reasonable set of evidence, and in some cases strong evidence, that environmental chemicals are likely to play some role in these conditions (Diamanti-Kandarakis et al. 2009). We are unable to calculate the exact contribution of chemicals for many of the cases of unknown etiology because most chemicals in commerce have not been tested sufficiently for reproductive and developmental health impacts tested and little information is available about where most chemicals are used and how the public may be exposed. (US Government Accountability Office 2005).

2) How does this trend correlate with the increased use of birth control pills and other menstrual modulators? Did you also account for the increase in obesity and other factors that affect human hormonal function?

The data that was discussed in my testimony on difficulty in conceiving and maintaining pregnancy comes from the National Survey of Family Growth, which is administered by the National Center for Health Statistics, Centers for Disease Control and Prevention (National Center for Health Statistics 2010). Periodically, NCHS surveys the population on certain reproductive health issues. For this particular question, they ask the individual woman if she has had difficulty in conceiving or maintaining pregnancy over the last 12 months.

A comprehensive review published in the peer reviewed literature concluded that while cessation of oral contraceptive use may delay time to conception, this delay appears to be temporary and only occurs in the early months (Barnhart and Schreiber 2009). The authors conclude that return of fertility is similar to other forms of contraception including condoms and natural family planning (Barnhart and Schreiber 2009).

Obesity has been identified as a risk factor for infertility and obesity has increased in the population, though it has appeared to level off in recent years (Ogden et al. 2007). As obesity has increased so has the production of certain environmental chemicals linked to infertility (Federal Reserve Board 2008). These (and other) risk factors for infertility can act independently or interact together, and more research is needed to understand their exact roles. A growing body of evidence is beginning to shed light on some of these potential inter-relationships. For example, there may be a relationship between exposure to certain environmental chemicals and obesity (Diamanti-Kandarakis et al. 2009; Grun and Blumberg 2007; Newbold et al. 2007). Specifically, obesity has been proposed to be another adverse consequence of developmental exposure to endocrine disrupting compounds, and experimental research by the National Institute of Environmental Health Sciences supports the idea that brief exposure early in life to environmental endocrine disrupting chemicals, especially those with estrogenic activity like diethylstilbestrol (DES), increases body weight as mice age.(Newbold et al. 2007). More research is needed to understand the applicability of these animal data to human health.

3. You say in your testimony that infants are at risk. Has infant mortality actually increased or decreased over time? Please cite your references.

Infant are at increased risk because there has been an increase in the percent of infants born premature (prior to 37 weeks of gestation) and born low birthweight over the past 10 to 20 years (Donahue et al. 2010; Davidoff et al. 2006; Martin et al. 2009; Institute of Medicine 2007). One out of every eight babies is born prematurely, a rate that has increased 36% since the early 1980s (Martin et al. 2009). Recent studies find that changing demographics and medical practice cannot explain the increases in preterm birth and low birthweight (Donahue et al. 2010; Davidoff et al. 2006). Premature birth and low birthweight can increase the risk of a number of infant mortality and morbidity conditions, including acute respiratory, gastrointestinal, immunological, central nervous system, hearing and vision problems, and childhood diseases, including learning and behavioral problems and developmental delays (Institute of Medicine 2007; Bhutta et al. 2002).

In addition, infants can be at increased risk because of their exposures to environmental chemicals that can occur prenatally and after birth. As noted by the President's Cancer Panel 2008-2009 report, authored by appointees of President George W. Bush, "numerous environmental contaminants can cross the placental barrier; to a disturbing extent, babies are born "pre-polluted" (President's Cancer Panel 2010). Both the panel and reviews of the scientific literature indicate that exposure during these important developmental windows can increase the risk of subsequent disease (Crain et al. 2008; Diamanti-Kandarakis et al. 2009; President's Cancer Panel 2010), thus putting infants at higher risk of adverse health outcomes from exposure to environmental chemicals.

Infant mortality declined between 1983 to 2000 from 10.9 per 1,000 live births to 6.9 per 1,000 live births (Federal Interagency Forum on Child and Family Statistics 2009). However, the US infant mortality rate did not decline significantly between 2000 and 2005, as discussed in a report from the National Center for Health Statistics (MacDorman and Mathews 2008). NCHS notes that the 2000–2005 plateau in the U.S. infant mortality rate is the first period of a sustained lack of decline in the U.S. infant mortality rate since the 1950s (MacDorman and Mathews 2008). The rate in 2006 is 6.71 per 1,000 live births (MacDorman and Mathews 2008). In addition, the US Government Health People 2010

target for goal for US infant mortality is 4.5 infant deaths per 1,000 live births, and the current US rate is about 50% higher than that goal (U.S. Department of Health and Human Services 2000). In 2004 (the latest year that data are available for all countries), the United States ranked 29th in the world in infant mortality, tied with Poland and Slovakia (National Center for Health Statistics 2007).

4. You say in your testimony that infants are at risk. Has infant mortality increased or decreased over time? According to the National Center for Health Statistics, National Vital Statistics System, the rate dropped from 10.9 per 1,000 births in 1983, to 6.7 per thousand births in 2006. Are they inaccurate?

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4. In your testimony you state that the incidence of gastroschisis has increased by over 300%. In the study you cite, the overall prevalence was reported to be 2.6 cases per 10,000

births, which is 0.026% of births. Does that mean that cases increased from 0.008% of births to 0.026%? Being that the most significant increase was among very young women, how do you attribute the cause of gastroschisis to chemical exposures?

The study about the increase in gastroschisis in California was published by Vu et al. and reports an overall prevalence of gastroschisis of 2.6 cases per 10,000 births (Vu et al. 2008). This is the overall prevalence of gastroschisis in their study population, which covered the years 1987 to 2003. In other words, this prevalence represents all the births and birth defects over the time period, not the prevalence in 2003. The authors performed a statistical analysis to assess the trend in gastroschisis over the time period, while accounting for other factors that may influence the trend, such as age of the mother and race. This means the authors can account for, for example, the changes in maternal age at birth, over the time period. After they take into account these demographic changes over time, they find that "the birth prevalence increased 3.2-fold (95% CI, 2.3-4.3) during the 17-year study period." This means that the birth prevalence increased 3.2 fold – or about 300% - between 1987 to 2003.

The authors note that other studies have found increases in gastroschesis in Utah, New York and North Carolina (Salihu et al. 2003; Laughon et al. 2003; Hougland et al. 2005). I discussed gastroschisis in my testimony as one of several reproductive health conditions that have been observed to be increasing over the past 1 to 2 decades either in the US or as reported for certain states. This illustrates an overall pattern of changing trends in disease and the papers cited indicate a need for further assessment of factors that can contribute to these increases. The influence on these diseases is multi-factoral, meaning that there can be a number of different risk factors that can contribute to disease, either independently or in concert. Environmental chemicals is one of the risk factors that can contribute to adverse reproductive health outcomes, and has been suggested in several of the articles as an important etiologic factor that requires further evaluation (for example, Vu et all notes "future studies are indicated to better examine the potential role of environmental factors in the risk for gastroschisis and gene-environment interactions.").

That gastroschisis is increasing among younger mothers is of concern, as we expect these mothers to have more healthy pregnancies. Data from the Federal Reserve Board show increase in chemical production in the US (Federal Reserve Board 2008). What is of concern is that younger women, more likely born during the time of higher chemical production, than in the past, could be at higher risk than their same age predecessors. Further study and data on environmental chemicals are needed to identify their potential role. Requiring comprehensive testing of chemicals on the marketplace as well as information about where people may come into contact with them is imperative to answer these questions and has been identified as a high priority for the federal government (US Government Accountability Office 2005, 2009).

5. You cite a lot of studies in your testimony. Are any of the studies you cite designed to determine the cause of a disease, or are they mainly associative studies?

To evaluate whether a chemical, or any other intrinsic or extrinsic factor, can increase the risk of disease requires evaluating available scientific information. Typically the type of information that informs whether there is a plausible link between an environmental chemical and increased risk of disease includes data from animal studies and human epidemiologic studies. Information from each of these data sources is used to identify

whether chemicals have the ability to increase risk of adverse health effects. Animal studies are particularly useful in an environmental health context, as they do not require direct human experimentation for information about the potential toxicity of chemicals.

Animals have long been used to understand the effects of chemical exposure on human reproduction and development (Holson et al. 2000). One of the first studies to use animals for reproductive and developmental assessments dates to a 1919 a study of the effects of alcohol on rats (Arlitt 1919). The reliability of experimental animal data for reproductive and developmental health has been well established and presently, there is no example of a chemical agent that has adversely affected human reproduction or development but has not caused the same or similar adverse effects in animal models (Nemec et al. 2006). Multiple studies on concordance have been performed of reproductive and developmental effects between animals and humans after exposure to a variety of chemical agents (Nemec et al. 2006; Hemminki and Vineis 1985; Kimmel et al. 1984; Newman et al. 1993; Nisbet and Karch 1983). One of earliest and most thorough is a technical report from 1984 for the National Center for Toxicological Research. This study, along with others, concluded there is concordance of developmental and reproductive effects and that humans are as sensitive or more sensitive than the most sensitive animal species (Kimmel et al. 1984). The National Academy of Sciences noted the importance of this report as it was the "first to utilize criteria of acceptance for both human and experimental animal reports that included study design and statistical power considerations." (National Research Council 2000).

Human epidemiologic studies of environmental chemicals provide the most direct evidence of the relationship between exposure and increase risk of adverse health outcomes, and are often the basis of regulatory and policy decision-making. Studies are typically designed to evaluate whether the change in the risk factor of interest, or the chemical exposure, is related to the change in the incidence or prevalence of the disease of study, while at the same time accounting for factors that may influence that relationship. For example, the studies that were used to determine that cigarette smoking was a risk factor for lung cancer evaluated whether men who smoked more had a higher risk of lung cancer. The conclusion that cigarette smoking caused lung cancer was based on this type of human epidemiologic studies, and as such, considering the studies can provide evidence that a chemical can contribute to the risk of disease. However, human epidemiologic studies require that we wait for people to develop clearly identified diseases from exposure, and thus are not an optimal public health approach.

There is uncertainty in the science, as science is always incomplete. As noted by Sir Bradford Hill, the epidemiologist who determined that cigarette smoking was a risk factor for lung cancer "*All scientific work is incomplete - whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time. (Hill 1965) Sir Bradford Hill 1965 address to the Royal Society of Medicine.*

Authoritative bodies that review evidence to evaluate whether certain chemical exposures can increase the risk of adverse health outcomes often rely on a graded scale of evaluation to acknowledge the uncertainty in the science while still allowing sufficient evidence for decision making. Such is the case for evaluating chemicals that can contribute to cancer, and authoritative bodies such as the International Agency for Research on Cancer and USEPA have approaches that integrate findings in animals and humans to arrive at an

assessment of the potential of a chemical to increase the risk of cancer (such as known, likely, possible, suggestive, etc.).

Finally, it is important to understand the potential risks of exposures to environmental chemicals are largely unintentional and as such, intentionally exposing individuals, particularly pregnant women and children, to chemicals to identify whether there are adverse health effects would be considered unethical.

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