Potential effects of real life exposure to environmental contaminants on reproductive health

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disruptors can cause an increase in adult onset disease such as infertility, prostate, ovary and kidney disease, cancers and obesity. Interestingly, this effect is transgenerational (F_1, F_2, F_3, and F_4 generations) and hypothesized to be due to a permanent (imprinted) altered DNA methylation of the germ-line. The transgenerational epigenetic mechanism appears to involve the actions of an environmental compound at the time of sex determination to permanently alter the epigenetic (i.e., DNA methylation) programming of the germ line that then alters the transcriptomes of developing organs to induce disease susceptibility and development transgenerationally. A variety of different environmental compounds have been shown to induce this epigenetic transgenerational inheritance of disease including: fungicide vinclozolin, plastics BPA and phthalates, pesticides, DDT, dioxin and hydrocarbons. The suggestion that environmental factors can reprogram the germ line to induce epigenetic transgenerational inheritance of disease and phenotypic variation is a new paradigm in disease etiology that is also relevant to other areas of biology such as evolution.

8 Environmental effects on programming of reproductive behavior. Frederick vom Saal*, *University of Missouri-Columbia, Columbia, MO.*

Fetal development is a period of heightened sensitivity to hormones that regulate the differentiation of tissues. An example showing that very small differences in testosterone (T) and estradiol (E_2) during fetal life can lead to changes in the life history of males and females is the intrauterine position phenomenon or IUP. Developing between fetuses of the same or opposite sex in species in which there are multiple fetuses (polytocous species) results in very small differences in fetal serum T and E_2 and differences in the development of tissues, including the brain, responsive to these sex steroids. For example, in mice, 2F males (located in utero between 2 females) have elevated serum E_2 during fetal life and in adulthood show an increase in sexual behaviors relative to 2M males (located between 2 males); 2M males have elevated serum T during fetal life and in adulthood are more aggressive than 2F males. Similarly, 2F female mice are more sexually attractive to males and more sexually receptive, but less aggressive, than their 2M female siblings. There are now numerous environmental chemicals that have been found to bind to estrogen receptors and disrupt normal estrogen signaling. The best studied of these estrogenic endocrine-disrupting chemicals is bisphenol A or BPA. Developmental exposure to BPA has been related to numerous changes in brain structure, function, and behavior in both males and females. Of great interest is the finding that the magnitude of the sex differences in some behaviors observed in untreated rats and mice is reduced or eliminated as a result of exposure to doses of BPA that are relevant to exposures experienced by humans based on biomonitoring studies. While there is less information regarding the effects of endocrine disrupting chemicals such as BPA in farm animals relative to rodents or humans, there is evidence for effects of fetal exposure to BPA on neuroendocrine function in sheep. There is also evidence for transgenerational transmission of altered phenotype, including behavior, caused by exposure to endocrine disrupting chemicals during the period of germ cell epigenetic programming.

Key Words: endocrine disruptor, bisphenol A, fetal programming

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While much research has focused on the effects of individual chemical exposures on animal health, far less is known about the effects of exposure to the mixtures of chemicals often found within our environment, even though this is a more typical exposure pattern. Biosolids (processed human sewage sludge) contain low individual concentrations of an array of contaminants including heavy metals and organic pollutants [e.g., polycyclic aromatic hydrocarbons, polychlorinated biphenyls and polychlorinated dibenzo(p)dioxin and furan] and form the basis of our model with which to study the effects of exposure to mixtures of environmentally relevant concentrations of pollutants in a domestic animal, the sheep. Studies using this model have investigated the effects of developmental exposure to biosolids on a variety of reproductive endpoints, including GnRH, kisspeptin, and estradiol receptor expression within the hypothalamus, LH and estradiol receptor expression within the pituitary gland, and protein, mRNA, and gamete production within the gonads of male and female sheep. The studies suggest that exposure to biosolids in utero, via maternal exposure, has detrimental effects on the fetal hypothalamo-pituitary-gonadal axis that could affect subsequent fertility. Studies with adult animals, also exposed during fetal life, suggest long-term effects of environmental chemical exposure on the reproductive axis. Investigation of lambs born to ewes grazed on biosolid-treated pastures (1) throughout life, (2) up until gestation, or (3) only during gestation have shown that some effects of environmental chemicals (relative to unexposed controls) may be more pronounced when exposure is acute, or that physiological compensation may occur when exposure is prolonged. Overall, the results of this study question the reliance on no observed adverse effects levels, with regard to chemical safety, when chemical exposure normally occurs as complex mixtures. The results suggest that developmental chemical exposure may affect the hypothalamo-pituitary-gonadal axis at a variety of levels, although whether the effects are driven by central effects or occur at each organ studied remains to be determined. [Wellcome Trust grant 080338].

Key Words: endocrine-disrupting chemicals, environmental contamination, ruminant