INTRODUCTION

Subfertility is a world-wide problem, affecting as many as 10 million US couples. Of the ~1.2 million couples actually examined, the male is the sole or partial cause of the problem 40% of the time (1). This is likely an underestimation of the real percentage linked to a male factor because of unsophisticated analyses of sperm quality. It has been estimated that 98% of male 'subfertility' cases result from compromised sperm quantity and/or quality while only 2% result from inadequate ejaculatory function (2). Over the past few decades, dozens of reports in the peer-reviewed literature have touted declines in semen quality in men, citing significant reductions in sperm concentration (number/ml), total sperm count (number / ejaculate), semen volume, sperm motility, sperm morphology, etc. These published "trends" have been linked to exposure to environmental chemicals, most popularly known as endocrine disruptive chemicals (EDCs), chemicals that mimic or interfere with endocrine signaling. Moreover, it has been suggested that exposures to EDCs during reproductive development may be causally related to other effects including reproductive tract malformations such as hypospadias, cryptorchidism, and predisposition to testicular cancer or ejaculatory dysfunction (3-4). Collectively, these observed human phenotypes have been referred to as the testicular dysgenesis syndrome (TDS).

It is inherently difficult to demonstrate a meaningful link between an environmental exposure and male subfertility in men but nonetheless an attempt must be made to determine environmental causality because, unlike genetically based infertility, chemically induced infertility may be preventable or reversible. Fortunately, while numerous environmental, occupational, and therapeutic agents have been identified as male reproductive toxicants in typical rodent models such as mice and rats, relatively few have been shown to cause similar effects in human males. Toxicology studies are designed with defined exposures administered

over a range of doses (5). There are many published studies relating male reproductive effects to exposures that target male germ cells at specific stages of development, the supporting Sertoli cells, as well as the endocrine support of spermatogenesis and sperm maturation (6–12). The concern that exposure of humans to EDCs during reproductive development may result in adverse reproductive phenotypes is fostered by the growing awareness that exposures of animals during fetal development can significantly alter male reproductive tract development and reproductive competence at adulthood (13-15).

Naturally, any meaningful discussion of male reproductive toxicology must be predicated on a solid understanding of male reproductive biology. For this reason a significant portion of this chapter focuses on normal facets of sperm production and sperm maturation, and the reliance of these functional outcomes, as well as male reproductive development itself, on a normal endocrine environment. The chapter ends with an attempt to summarize the state of the epidemiology literature in the male and offer recommendations for significant improvements in the conduct and coordination of toxicology and epidemiology studies.

OVERVIEW OF MALE REPRODUCTIVE BIOLOGY

The Testis

The following overview is derived in large part from earlier reviews (5, 16-17). The production of functional sperm in numbers adequate for successful fertility and fetal development occurs within seminiferous tubules in the testis (Figure 1A). In cross section the tubule consists of a lumen and the seminiferous epithelium resting on a basement membrane (Figure 1B and C). The process of spermatogenesis commences when a spermatogonial stem cell enters the germ cell lineage in the most basal aspect of the epithelium, just above the basement membrane (Figure 1D). The type A1 spermatogonium is now committed to complete