5 Introduction and objectives

Phthalates are economically important chemicals used primarily as plasticizers to impart flexibility to polyvinylchloride (PVC) plastics. (Kavlock et al., 2002; Shea, 2003). They are present in a wide variety of products, including building materials, food packaging, clothing, toys and medical devices. Di-(2-ethylhexyl) phthalate (DEHP) is currently the most commonly used phthalate accounting for approximately 50% of the market for PVC plasticizers in Western Europe (SCMPMD, 2002). However, DEHP and other phthalates are not covalently bound to the plastic matrix and can easily leach out to contaminate the external environment (Petersen and Breindahl, 2000). According to biomonitoring studies, the general population is ubiquitously exposed to DEHP (Koch et al., 2003, 2006).

Recent animal toxicity studies indicate that exposure to certain phthalates like DEHP and di-(butyl) phthalate (DBP) results in severe effects on the developing male reproductive system (Mylchreest et al., 1998; Gray et al., 1999, 2000). Male offspring of rats exposed to high DEHP doses (e.g. 750 mg/kg/day) during gestation or gestation and lactation display reproductive tract abnormalities compatible with disruption of androgen-dependent development and impaired testicular function (Gray et al., 2000; Moore et al., 2001). These alterations are believed to be downstream consequences of altered Sertoli and Leydig cell functions in the developing testis (Sharpe, 2001; Fisher et al., 2003; Foster, 2006). However, most experimental studies with DEHP have tested only high doses which are believed to be irrelevant for actual human exposures.

Traditional toxicity studies are based on the general assumption that dose-response relationship for noncarcinogenic chemicals is monotonic and presents a threshold, i.e., the assumption that a level of exposure exists for below which no effect can be observed (Zenick and Clegg, 1989; Faustman and Omenn, 1996). As a consequence, animal toxicity tests and mechanistic research typically use doses that are well above the low environmental exposures of humans. In addition, the possibility of nonmonotonic (biphasic) dose-responses is generally ignored. The objective of the present study was to determine the effects of in utero and lactational DEHP exposure on reproductive development and function of male offspring rats. A large number of low (human relevant) and high doses was used to adequately characterize the dose-response relationship for different endpoints.