(Hoymann 2007). Monitoring of respiration rate, oxygen saturation, and arterial blood gases may be included in general toxicity studies to provide some indication of pulmonary dysfunction.

With regard to morphological organ damage, histopathology of the lungs in the general toxicity studies is a very sensitive method. In addition, bronchoalveolar lavage may be added in order to have some mechanistic readout (Henderson et al. 1985).

10 Developmental Toxicity

Reproductive toxicity including teratogenicity and embryo-fetal toxicity is important, when drugs are intended for use in a woman of child-bearing potential. According to regulatory guidance, such data are only needed prior to entering longer-term clinical studies or use in larger patient populations in those cases, where adequate contraception can be used. In addition, such effects may often be acceptable for drugs when adequate precautions are taken to hinder the treatment of pregnant women (e.g., adequate labeling, risk-management plan).

However, for drugs in some indications, such effects result in termination of the development (e.g., in fertility control). In such cases, early screening for developmental toxicity may be needed. Reproduction is a very complex process. There was extensive research to identify adequate nonanimal methods to predict reproductive toxicity, mainly because of the need to classify a high number of chemicals. Since reproductive toxicity studies require a high number of animals, in vitro systems were urgently needed. However, some aspects cannot be mimicked in vitro. In silico prediction is currently also not advanced enough to allow meaningful prediction.

Nevertheless, several in vitro screening systems have been developed, which may also have some value in the early screening of drug candidates. These include the rodent whole-embryo culture test and the embryonic stem cell test (Brannen et al. 2011). The mouse embryonic stem cell test (mEST), which has the differentiation of pluripotent stem cells into beating cardiomyocytes as endpoint, has already been validated by ECVAM, but the predictive value is still uncertain, as a second data set did not confirm the initial positive results. For the mEST, a high-throughput screening method was developed. The second test, the rat whole embryonic cell culture (rWEC), allows evaluation of multiple organ systems, but it is labor intensive and time consuming and thus, more suitable for mechanistic investigations than early screening (Van der Laan et al. 2012). In addition, a human embryonic stem cell assay (hEST) called DevTox was developed, which may help in screening some aspects of developmental toxicity (West et al. 2010). Zebrafish larvae may also be used as a screening tool allowing evaluation of some aspects of developmental toxicity (Chapin et al. 2008; Sukardi et al. 2011).

The traditional developmental toxicity assays in rodents and non-rodents are still the relevant assays to predict potential developmental toxicity and teratogenicity, but the assays are quite time consuming and need a rather high number of animals,