

**Table 1** Species-Specific Toxic Effects (4). Reprinted with Permission

Type of toxicity	Structure	Sensitive species	Mechanism of toxicity
Ocular	Retina	Dog	Zinc chelation
Ocular	Retina	Any with pigmented retinas	Melanin binding
Stimulated basal metabolism	Thyroid	Dog	Competition for plasma binding
Tubular necrosis	Kidney	Male rats	Androgen-enhanced sensitivity
Urolithiasis	Kidney and bladder	Rats and mice	Uricase inhibition
Teratogenesis: fetal mortality	Fetus	Rats and mice	Uricase inhibition
Cardiovascular	Heart	Rabbits	Sensitivity to microvascular constriction

#### 4. FACTORS THAT CAN INFLUENCE STUDY RESULTS

Variables that can affect the outcome of studies intended to examine preclinical exposure–response relationships include the following (7).

- *Weight*: Animals of the same weight may have differences in lean tissue mass.
- *Age*: Age does affect sensitivity for some drugs in some species, including humans.
- *Sex*: Females of some species can exhibit more (or less) frequent toxic effects as compared to males.
- *Time of Administration*: Considerations include period of fasting, gastric emptying rate, and diurnal rhythms.
- *Temperament*: Stressors may cause a constriction of the splanchnic visceral blood vessels, which can affect drug metabolism and the proportion of the total cardiac output reaching the peripheral tissues.

Animal age is an important consideration when conducting toxicological studies to support drug use in human pediatric populations. The age of the animal used as the toxicological test species should be consistent with the intended age of the targeted human recipients due to potential differences in drug disposition and action, metabolism, body composition, receptor expression, and organ function that may occur in juveniles vs. adults. This issue is discussed in detail later in this chapter.