The rate of false positives in monkeys was slightly less than that of dogs. Cases where neither species expressed toxic reactions seen in humans were rare, although examples of renal, cardiovascular, and neuromuscular toxicity do exist.

With regard to rats, basic human–rat differences in physiology may affect study outcome. Unlike humans, rats can synthesize ascorbic acid, have no gall bladder, are coprophagous, are obligate nose breathers, and have important differences in their lung function and morphology (17). Moreover, when rodents are treated with antimicrobial agents, they frequently develop cecal dilation and torsion due to alterations in their intestinal flora. This finding may preclude their use as models for development of these drugs. Monroe and Mordenti (17) have summarized the physiological, anatomical, and biochemical factors that can be considered in preclinical studies when analyzing data from studies that employ rats as the target species. Their summary is reproduced in Table 3.

Strain of animal may also affect study outcome. For example, there is greater tobramycin toxicity observed in Fischer rats as compared to Sprague–Dawley rats (18). Differences in toxic responses between species of monkeys are also evident. Stump-tailed macaques exhibit the same thrombocytopenia as that seen in humans with compound BL-4162. However, neither the rhesus monkey, cynomolgus monkey, squirrel monkey, nor the chimpanzee exhibit that same toxic effect (15).

Conditions associated with animal care, such as crowding, isolation, temperature, food or water restriction, alteration of light–dark cycle, immobilization, handling, and drug administration procedures, can result in physiological changes that are not drug related. Each of these conditions can alter the release of hormones such as adrenal corticotrophic hormone, thyroid hormone, insulin, and many of the pituitary hormones. In turn, the latter can modify responses to the various toxicants (4,19).

The dose–effect relationship can also be influenced by normal diurnal rhythms. For example, both hepatic and renal functions exhibit diurnal variation in mice. Metabolism is higher during the active dark phase as compared to the light phase (20). Significant circadian-related fluctuations in drug pharmacokinetics have been observed for a wide variety of drugs including antimicrobial compounds, neurological and psychiatric drugs, anti-inflammatory drugs and cardiovascular agents (21). There can be marked diurnal variability in disease expression and drug therapeutic activity (22–24). Similarly, the magnitude of drug toxicity may vary as a function of administration time (25–27). In some cases, circadian variability in drug toxicity has been attributable to fluctuations in the activity of certain metabolic pathways (27), and these variations may not be equally expressed in males and females (28).

Fasting can alter drug pharmacokinetics. In addition to the relationship between prandial state and such factors as gastric emptying, drug