dissolution, enterocyte permeability, and hepatic blood flow (29,30), fasting itself can significantly affect the level of several metabolizing enzymes. In some cases, cycles in eating activity are responsible for the apparent circadian variability in drug pharmacokinetics (31). Partial dietary restriction was found to exert a protective effect against certain types of carcinogens. When fed 75% of ad libitum intake, rats were found to have a significant reduction in certain types of tumors (i.e., pituitary adenomas, hepatic foci) as compared to animals provided food ad libitum (32).

The composition of the animal diet can also influence the response to toxic agents. Rats fed diets deficient in vitamin A or beta carotene produced significantly higher rates of malignant tumor formation in response to exposure to aflatoxin B1. However, diets containing 10 times the normal levels of vitamin A did not result in a protective effect above that observed under control conditions (32).

Dietary fats themselves may affect drug pharmacokinetics (33,34). This variable may influence the results of toxicological studies since prior to oral administration in rats, lipophilic compounds are frequently dissolved in dietary vehicles such as corn oil, olive oil, or sesame oil. While these vehicles do not appear to significantly alter drug metabolism when administered in an amount consistent with that used during experimental dosing, significant changes were found to occur in the levels of certain microsomal enzymes (e.g., increased CYP 3A and decreased CYP 2C11). Accordingly, the possibility that these dietary oils may influence hepatic CYP-mediated drug metabolism or exacerbate certain CYP-mediated drug–drug interactions cannot be discounted (34).

In response to concerns regarding the influence of dietary fats on the outcome of toxicological studies when used as gavage vehicles, the National Institutes of Health sponsored a study comparing the toxic effects of corn oil, safflower oil, and tricaprylin (35). Each gavage dose was administered at volumes of 2.5, 5, or 10 mL/kg daily for 5 days per week for a total of 2 years. Observed effects of these oils included hyperplasia and adenoma of the exocrine pancreas, a decrease in the incidence of mononuclear cell leukemia, and a reduction in the incidence or severity of nephropathology in male rats. There was also an increase in the incidence of squamous cell papillomas of the forestomach of rats receiving 10-mL tricaprylin/kg. For the most part, this investigation demonstrated that all three oils were capable of causing dose-related toxicities, and that it is the level of fat rather than the degree of saturation that is the most important consideration in this regard.

In a two-year study where a 500 mg total dose of dichloromethane was administered in corn oil (2.5, 5, or 10 mL/kg) to male rats, the use of a corn oil vehicle substantially reduced the highly toxic effects associated with dichloromethane. When administered without corn oil, the dichloromethane group exhibited severe toxic reactions. However, rats survived the 2-year