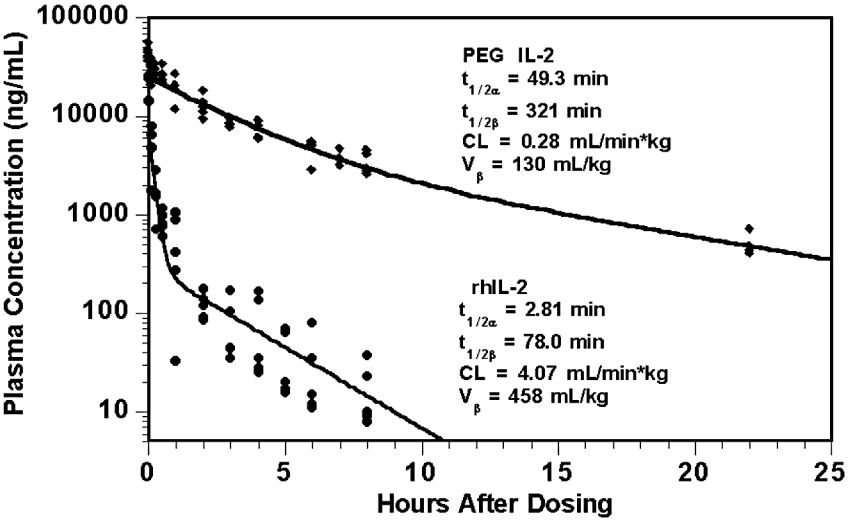

Figure 14 Pharmacokinetics of recombinant human interleukin-2 (rhIL-2) and its PEGylation form (PEG IL-2) in rats after IV bolus administration of 0.25 mg/kg. The data were described by a linear two-compartmental pharmacokinetic model.

9. IMMUNOGENICITY

Immunogenicity is the ability to induce the formation of antibodies, a prerequisite for antigenicity, which is the ability to react with specific antibodies. Immnogenicity is an important property distinguishing most biologic products from most small drug molecules. An immunogenic response to heterologous (nonhost) proteins is expected, as antibody formation is also often observed after chronic dosing of human proteins in animal studies. However, recombinant human proteins may also stimulate the production of circulating antibodies in chronic human therapy and clinical studies. In this case, immunogenic responses are sometimes associated with the formation of protein aggregates, altered proteins forms or fragments, such as acetylated protein or proteins with broken disulfide bridges (for interferons, for example). In other cases, impurities from cell substrates or media components are either directly immunogenic or act as adjuvants to stimulate antibody formation against the protein.

Immunogenic responses can cause a wide variety of unwanted effects, with different degrees of severity. Safety issues include the potential for injection site reactions, systemic hypersensitivity reactions, and anaphylactic shock in some cases. As an example, bovine Cu, Zn-superoxide dismutase (Cu, Zn-SOD) (Orgotein) as a treatment for various arthritic diseases was withdrawn from several European countries because of hypersensitivity.