molecular weight (55). After lymphatic absorption, compounds circulate within the lymph and are gradually returned to the blood. As a result, lymph concentrations for these proteins may be higher than blood concentrations. Targeting of the lymphatics may be beneficial for proteins that act on the immune system, such as for IL-2. It was shown that s.c. administration of IL-2 in a pig model resulted in higher lymph levels as compared to blood, and at higher doses, absorption was exclusively through lymph (56). The IL-2 receptor-positive T-lymphocytes, that are thought to be primarily associated with efficacy, reside largely in the lymphoid organs. On the other hand, natural killer cells and neutrophils in blood produce cytokines, reactive oxygen intermediates, and proteases, all of which have been shown to be necessary to produce IL-2 toxicities. Therefore, adverse in vivo activity of IL-2 may be related to blood levels, while beneficial activity may be associated to lymph concentrations (56).

Biodistribution into target organs, usually receptor-mediated, is important for the pharmacodynamics of protein drugs. For some proteins, saturable receptor-mediated tissue uptake in target organs is responsible for nonlinear kinetics (57). For example, the uptake clearance of rhEPO by bone marrow and spleen exhibited clear saturation in rats. Also, a single high dose of rhEPO caused a reduction of uptake clearance by bone marrow and spleen, while repeated injections caused an increase of the tissue uptake clearance, especially by the spleen, in a dose-dependent manner (57). Hematopoietic parameters such as hematocrit and hemoglobin concentration changed accordingly, suggesting that changes in the uptake clearance were caused by down- or upregulation of EPO receptors.

4. PLASMA PHARMACOKINETICS

Although the time course of the compound at the receptor or effector site is the desired knowledge to predict or explain the pharmacodynamics (PD), accurate drug level data at that site are difficult to obtain. In most cases, pharmacokinetic (PK) data are limited to plasma concentration data. Pharmacokinetic models are widely used to describe and predict the time course of the drug in plasma and tissues. These models include compartmental models and physiological models. A scan of the literature shows that mostly compartmental models are used, in particular one- or two-compartmental models. Terminal-phase elimination half-lives for small to medium sized protein drugs in humans range from a couple of hours (e.g., 3.7 hr for rt-PA) to more than 12 hr (e.g., 15 hr for Factor VIII). Very large protein drugs such as monoclonal antibody-based pharmaceuticals have plasma half-lives ranging from days to several weeks. The IgG1-based recombinant humanized monoclonal antibody trastuzumab (Herceptinα, 148 kDa) for example has a half-life that ranges from 1.7 days to 15 days after i.v. doses of 10 and 500 mg, respectively (58).