mixture interactions to affect chemical and drug disposition, pharmacokinetics, and activity has been well recognized for many years and is extensively reviewed elsewhere (4, 5, 9–13). Despite the widespread knowledge base of the importance of drug–drug interactions and the importance of chemical interactions in systemic pharmacology and toxicology, very little attention outside of the dermatological and transdermal formulation arenas have been paid to interactions that may occur after topical exposure to complex mixtures. The focus of this chapter is to overview the potential mechanisms operative in topical chemical mixtures, as well as to illustrate these interactions with data from our laboratory.

22.2 RISK ASSESSMENT

Dermal risk assessment of individual chemicals is based on knowledge of the permeability characteristics of specific chemicals through skin, with extrapolations being made to potential absorption in humans (14). Numerous contributions in the present text discuss this field. A great deal of emphasis is appropriately placed on calculating potential exposure, with less attention focused on the actual permeability of the exposed compound through skin, which is required to estimate systemic exposure. Collection of this latter data is preferably done in a controlled and validated laboratory animal model, although one could argue that even quality data in a laboratory rodent might not be optimal for predicting human skin absorption due to well-known species differences. Unfortunately, very little human data exist to support these estimates, and it is unethical to expose humans to hazardous materials to generate these parameters. When data are not present, extrapolations of potential absorption are made based on physical chemical parameters (e.g., molecular volume and water solubility) or surrogates such as partition coefficient (PC) (concentration ratio between vehicle and membrane) that correlates to permeability of individual chemicals primarily through in vitro skin models. These models and analyses are called quantitative structure permeability relationships (QSPRs). A great deal of effort has been spent on developing these permeability estimates. However, it is evident from a close review of these approaches that the combination of dermal absorption and mixture guidelines has not yet routinely occurred, despite broad acceptance that the skin is a primary route of exposure for many chemicals and that most chemical exposure occurs in mixtures.

It is impossible to assess all potential combinations of chemicals in order to determine which have the greatest potential to modulate absorption of a known toxic entity topically exposed in a chemical mixture. The present state of knowledge in this area is particularly weak, since the significance of specific interactions has not been quantified, let alone in many cases even identified. In many ways, this same concern continues to define the very nature of chemical mixture toxicology (5, 9, 10, 12, 13). In cases where the potential toxicity of a specific mixture is of concern (e.g., at a specific toxic waste site), the complete mixture is often tested (15). However, how does one quantitate the absorption of a mixture consisting of 50 chemicals? How are markers selected? How are these data expressed? Unfortunately, even after a complete toxicological profile of a specific mixture (e.g., "standard" mixture of 50 environmentally relevant compounds, surrogate jet fuels, etc.) is defined using all the techniques modern toxicology and toxicogenomics has to offer, one cannot define the links between absorption and the effects seen. Could the observed toxicity be exerted because a specific toxicant was in the mixture, because two synergistic toxicants were absorbed, or was it exerted simply by the presence of a mixture component (e.g., alcohol, surfactant, and fatty acid) that enhanced the absorption of a normally minimally absorbed toxicant? In this latter scenario, if the enhancer were not present, absorption would have fallen below the toxicological threshold. We have demonstrated such an interaction with the putative toxins involved in the Gulf War syndrome, where systemic pyridostigmine bromide or co-exposure to jet fuel was shown to greatly enhance the dermal absorption of topical permethrin (16, 17). Would other pesticides be similarly affected? How does one take into account such critical interactions so that a proper risk assessment may be conducted?

One recently reported approach to address this problem assesses potential interactions in dermal absorption by fractionating the effects of a vehicle on drug penetration onto the two primary