parameters describing permeation according to Fick's law: partitioning (PC) and diffusivity (D) [see later; permeability (K_p) = D × PC/membrane thickness] (18). Although this study only reported on four compounds, one (diazepam) was not predictable using this approach, as its physiochemical properties were already optimal for absorption, and only absorption enhancers were investigated. This study illustrates the difficulty of making broad generalizations across compounds solely on physical chemical properties.

A more inclusive approach to this problem is to define chemicals on the basis of how they would interact with other components of a mixture, as well as with the barrier components of the skin. What are the physical-chemical properties that would significantly modify absorption and potentiate systemic exposure to a toxicant? What are the properties of molecules susceptible to such modulation? Unlike pharmaceutical formulation additives in a dermal medication, chemical components of a mixture are not classified by how they could modulate percutaneous absorption of simultaneously exposed topical chemicals. They are either present functionally for specific purposes (e.g., performance additives, lubricants, and modulators of some biological activity), sequentially because they were applied to the skin independently at different times for unrelated purposes (cosmetic followed by topical insect repellent), accidentally because they were disposed of simultaneously as waste, or they are coincidentally associated as part of a complex occupational or environmental exposure.

22.3 MECHANISMS OF INTERACTIONS

Chemical interactions that may modulate dermal absorption can be conveniently classified according to physical location where an interaction may occur. The advantage of this approach is that potential interactions may be defined on the basis of specific mechanisms of action involved, as well as by the biological complexity of the experimental model required to detect it.

Surface of skin:

- Chemical-chemical (binding, ion-pair formation, etc.)
- Altered physical-chemical properties (e.g., solubility, volatility, and critical micelle concentration)
- Altered rates of surface evaporation
- Occlusive behavior
- Binding or interaction with adnexal structures or their products (e.g., hair, sweat, and sebum)

Stratum corneum:

- Altered permeability through lipid pathway (e.g., enhancer)
- Altered partitioning into stratum corneum
- Extraction of intercellular lipids

Epidermis:

- Altered biotransformation
- Induction of and/or modulation of inflammatory mediators

Dermis:

- Altered vascular function (direct or secondary to mediator release)

The first and most widely studied area of chemical-chemical interactions is on the surface of the skin. The types of phenomena that could occur are governed by the laws of solution chemistry and