conditions of exposure (e.g., apply heat or cover application area with plastic). An ingredient could be contained in one product intended for leave-on usage (e.g., moisturizing lotion) or in a different product intended as a rinse-off formulation (e.g., hair dye product or shampoo). All use conditions should be defined and considered for a relevant consumer exposure estimate.

A relevant dermal exposure estimate should be based on reliable information regarding the concentration of the ingredient in the finished product. However, this product information is usually proprietary and difficult to obtain. FDA laboratories, Cosmetic Ingredient Review (CIR), and other consumer groups occasionally conduct surveys that directly measure ingredient concentrations in finished cosmetic products. These specific ingredient concentrations can then be used in exposure estimate calculations.

The initial dermal exposure estimate is calculated from as many of the previously mentioned exposure conditions as are deemed pertinent to include. When actual data are unavailable for a specific parameter, an estimate of the parameter must be used. However, any estimates used in the calculation should be clearly noted in the exposure estimate summary. This is important, since uncertainties in the exposure estimate will affect the degree of confidence in the final safety assessment. It is desirable to calculate an exposure in units of ingredient weight/kilogram (kg) body weight/day. This helps to facilitate comparison of dermal exposure to a NOAEL obtained from a dietary or parenteral administration.

59.3.2 Percutaneous Absorption

Ideally percutaneous absorption is measured in fresh, viable human and/or animal skin using in vitro flow-through diffusion cell methodology. However, nonviable skin may be used if metabolic activity is not needed to characterize the absorption profile. These techniques are described in more detail in Chapter 51 of this book. A variety of receptor fluids may be used, the composition of which will depend upon the specific chemical being tested. The application of chemicals to skin should be made in a vehicle that approximates consumer use conditions as closely as possible to generate data providing realistic exposure estimates.

Skin absorption is dependent on many factors, including lipid solubility of the chemical, duration of skin contact, location of skin contact, vehicle for the chemical, environmental conditions, occlusion of the dosing area by clothing, surface area of skin application, and the age of the individual. These factors must be considered when attempting to accurately define the exposure estimate.

Skin absorption studies should be conducted under conditions that approximate specific product use/misuse conditions. A well-designed in vitro absorption study should consider the relevant experimental conditions necessary to replicate consumer use conditions. A typical experimental design should consider the dosing vehicle, the dosing concentration, and the duration of exposure to simulate use conditions (3). To simulate a leave-on product, the dosing solution may be left on the skin for 24 hours, whereas for a rinse-off product, the dosing solution may be removed after one to five minutes (4). The percentage of applied dose absorbed is experimentally determined and is used in estimating systemic exposure to the chemical.

59.4 SAFETY ASSESSMENTS

59.4.1 Noncarcinogenic Cosmetic Ingredient Safety Evaluation: Assume a Threshold for Toxicity

One approach for extrapolating data from animal studies to human hazard/safety is the safety factor approach. The safety factor approach implies that there is a threshold dose for a toxic effect. If the NOAEL is considered the threshold dose, then the NOAEL is divided by a safety factor (usually 100; 10 for interspecies [animal to human] and 10 for intraspecies [human]) variability to determine a safe human dose or an "acceptable daily intake" (ADI) (5).