# 24 Solvent and Vehicle Effects on the Skin

**Michael S. Roberts and Audrey Gierden**
*Department of Medicine, Princess Alexandra Hospital, University of Queensland, Woolloongabba, Queensland, Australia*

**Jim E. Riviere and Nancy A. Monteiro-Riviere**
*Center for Chemical Toxicology Research and Pharmacokinetics, College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina, U.S.A.*

## INTRODUCTION

The effects of solvents and vehicles on the skin are important since skin is the largest organ of the human body and provides protection against the external environment. In addition, the skin enables us to maintain a state of homeostasis. However, skin and its barrier properties may be altered when exposed to various chemical agents. Exposure to solvents and vehicles can occur after occupational or accidental spillage, topical application of cosmetics, sunscreens, insect repellents, as well as following the topical application of drugs for therapeutic purposes.

This chapter provides an update on our earlier work (1). As discussed earlier in this book, the outermost layer of the skin, the stratum corneum (SC), is the main skin barrier and is composed of keratinized dead epidermal cells that are thin, less than 1 μm, and 30 to 40 μm in diameter. Figure 1 shows a transmission electron microscopy (TEM) image of the SC (1). The lipid bilayers between the cells can be easily visualized by after fixing in Trump's fixative and postfixing in phosphate-buffered ruthenium tetroxide prior to being processed for TEM. Desmosomes are evident in lipid bilayers, especially in areas associated with friction in the environment. Disintegration of the desmosomes, most evident in the outermost SC, is frequently associated with the creation of lacunae (1). Desmosomes usually span the entire width of the intercellular space but, with jet fuel JP-8+100 treatment, desmosomes are degraded and separated from the central core leaving a space (lacunae) between the desmosomes (2), similar to what was found for hydrocarbon solvents in our earlier work (1). The lacunae are probably also due to the extracted lipid lamellae (1). The main lipids in the SC are ceramides, cholesterol, and free fatty acids (3).

## MECHANISMS BY WHICH SOLVENTS AFFECT SKIN PERMEABILITY

Figure 2 shows that solvents can cause a range of structural alterations when applied on the skin. In general, either the lipid bilayer or the SC proteins are affected. Solvents can selectively extract skin lipids from intercellular lamellae, corneocytes, or even the follicles, as illustrated in Figure 3A for cyclohexane. *n*-Octanol, laurocapram, isopropyl myristate, and oleic acid are able to extract ceramides; this would generate a dilatation between adherent cornified cells thus enhancing the intercellular penetration pathway. Figure 3B shows such an effect occurring after extraction by a cyclohexane:ethanol (4:1) solvent. Polar enhancers such as *N*-methyl-2-pyrrolidone (NMP) and dimethylsulfoxide (DMSO) partly


**FIGURE 1** A cross section of human stratum corneum showing corneocytes packed with keratin and intercellular lipid regions containing lipid bilayers and desmosomes (D), as well as degenerating desmosomes (*arrow*) that lead to the formation of lacunae (*double arrow*) ruthenium tetroxide postfixation (×48,750). *Source*: From Ref. 1.

extract sphingolipids (4). Some water-soluble solvents affect the intercellular lipid layers at or near the polar head group, disturbing the hydration spheres. Others act mainly between the hydrophobic tails of the lipids, causing their organization to be disturbed and increasing their fluidity (5). Some solvents also interact with the proteins, leading to a conversion of keratin from α-helix to β-sheet, often accompanied by the uncoiling of the filaments. Hygroscopic enhancers affect the integrity of desmosomes and other proteic junctions that maintain the SC cohesion, leading to fissuring and splitting of the corneocytes or squamous cells. In summary, it is most likely that solvent will interact with the SC components with multiple mechanisms.

The penetration of a solvent through the skin and its effects also depend on its characteristics such as its molecular weight (MW), lipophilicity, concentration, and viscosity.

Methyl groups are often associated with the greatest enhanced permeability of solvents. For example, solvents resulting in the highest permeability enhancements include: DMSO, NMP, dimethylformamide, and dimethylacetamide. Each has one or more methyl groups directly linked to heteroatom (S or N) (6). The extent of solvent effects depends on the duration and area of solvent contact, the body site, and whether the site is occluded.

## MECHANISM OF INDIVIDUAL SOLVENTS/PERMEATION ENHANCERS/VEHICLES

### Water

The effects of water on the skin are discussed by Roberts and Bouwstra in Chapter 7 of the companion volume (7). In brief, the effects of water occur mainly within the corneocytes due, in part, to its interaction with complex mixture of water soluble and compounds with a high affinity for water (called natural moisturizing factor) therein. While the lipid lamellae are relatively unaffected by skin hydration level, lacunae from desmosome degradation are filled with water in over-hydrated situations (8).

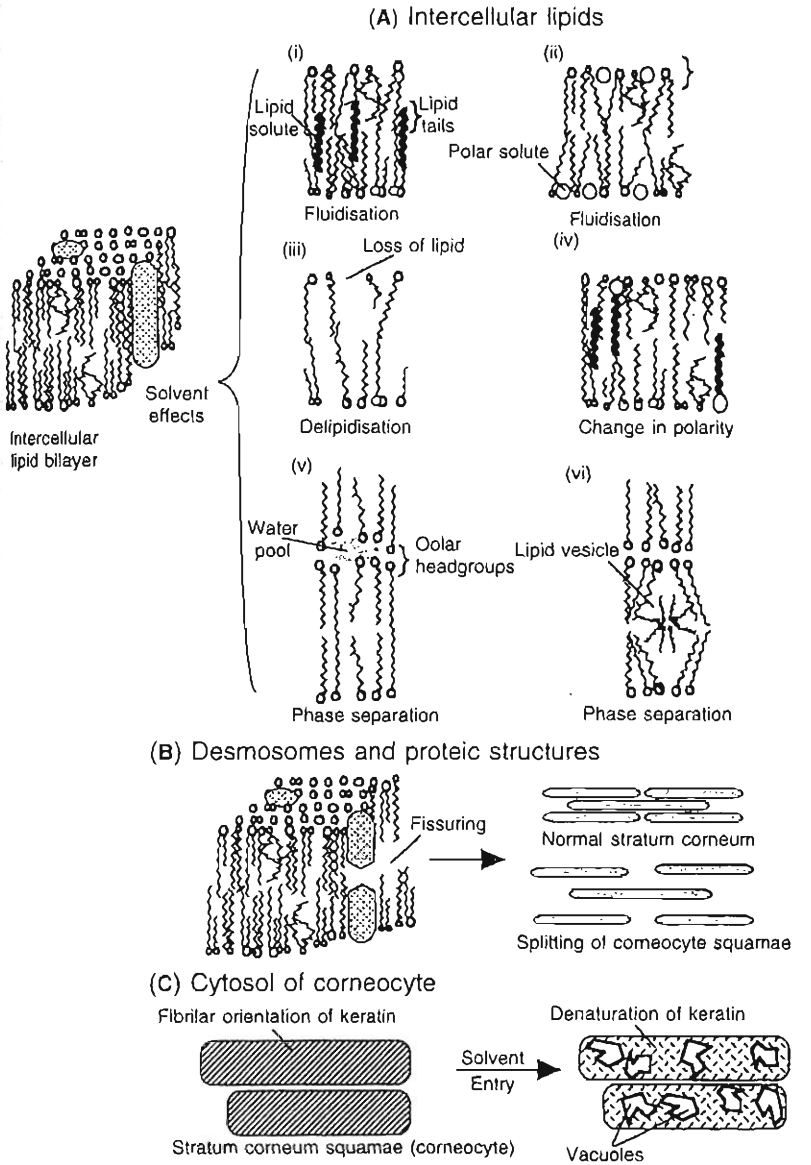
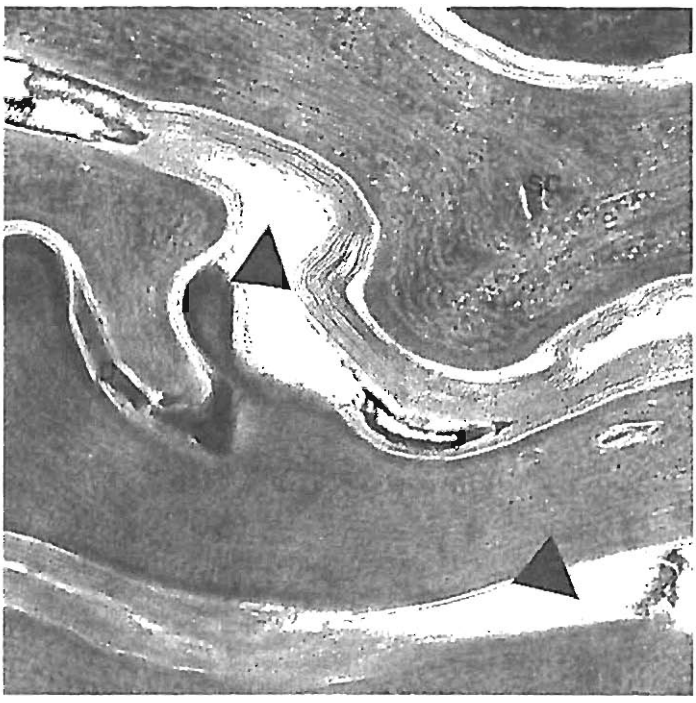


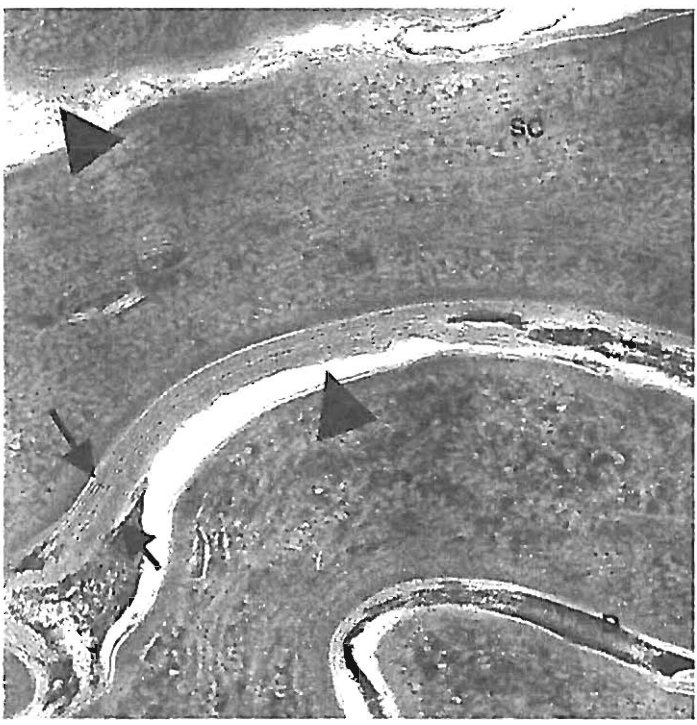

**FIGURE 2** Sites of Solvent action in the stratum corneum. (**A**) In the intercellular lipid layer, the processes involving the intercellular lipids include: (i) interaction of lipid solutes (lipophilic enhancers) with intercellular or corneocyte envelope lipids, resulting in increasing the fluidity of the lipid tails; and/or (ii) interaction of polar solutes (polar enhancers) with the polar head groups of the intercellular or corneocyte envelope lipids, increasing their fluidity; (iii) solvent extraction of lipid components; and/or (iv) solvents changing the polarity of the intercellular and/or corneocyte envelope lipids; (v) formation of water pools in the polar head group region; and (vi) forming of lipid vesicles in the lipid tail region. (**B**) Damage to the desmosomes and protein-like bridges may lead to a fissuring of the intercellular lipid layer and splitting of the corneocyte squamae. (**C**) Entry into the corneocyte may be associated with disruption of keratin and vacuolization. *Source*: Adapted from Ref. 1.

## Alcohols and Glycols

The alcohols and glycols are semipolar solvents which can have a range of effects on the skin. Ethanol can extract lipids from the SC and may displace bound water molecules at the lipid head group–membrane interface region thus promoting interdigitation of the hydrocarbon chains (4). It can also improve solute partitioning




(A)




(B)

**FIGURE 3** Transmission electron micrographs of SC showing: (**A**) areas (*arrowhead*) devoid of intercellular lipid between the SC layers due to extraction with cyclohexane; and (**B**) the intercellular space with compact lipid lamellae (*arrows*) and desmosome attachment (D). Large spaces (*arrowhead*) representative of devoid lipid lamellae caused by cyclohexane and ethanol (4:1) extraction (×140,300). *Abbreviations*: D, desmosomes; SC, stratum corneum. *Source*: From Ref. 14.

in the SC through its action in changing its solubility properties of the SC (9). In general, the enhancing abilities of alcohols depend on the number of carbon atoms in the chain (10). Propylene glycol competes with water for the Hbond binding sites thus solvating keratin and it intercalates itself in the polar head groups of the lipid bilayers (10). Glycerol is a humectant and, accordingly, glycerol-containing moisturizers produce long-lasting moisturization by binding and holding water. Glycerol can prevent humidity-induced crystal phase transitions in SC lipids. In addition, it can facilitate desquamation by promoting the proteolytic degradation of the corneodesmosomes and induce the maturation of corneocytes.

### Acetone

Acetone disrupts the organization of the lipid bilayer by selectively removing lipids from intercellular lipid domains (11). Acetone mainly removes nonpolar lipids such as sterol esters, free fatty acids, triglycerides, and alkenes and to a lesser extent polar sphingolipids and free sterols (12). The alterations in the intracellular domain caused by acetone are not uniform. Figure 4 shows that both acetone and ethanol leads to lipid extraction from the SC.

### Dimethylsulfoxide

DMSO is a powerful aprotic solvent that creates solvent-filled spaces when applied onto skin and, in concentrations above 60%, disturbs the lipid bilayer organization (10). DMSO also denatures protein and, when applied on human skin, leads to the intercellular keratin conformation changing from α-helix to β-sheet. DMSO further interacts with the intercellular lipids in the SC, distorting the packing geometry—probably by interaction with the head groups of bilayer lipids. After treatment with DMSO, highly enlarged intercellular space and expanded lacunae can be observed, with the desmosomes also appearing to be swollen (1).

### Pyrrolidones

NMP and 2-pyrrolidone (2P) are the most widely used enhancers of this group. Pyrrolidones can enhance penetration of both lipophilic and hydrophilic drugs (10). As pyrrolidones can cause adverse reactions, their clinical usefulness is limited (10).

### Urea and Derivatives

Urea is a natural moisturizing agent, which is present in the skin and, when applied in formulations, can swell the desmosomes in the SC layers and promote desquamation (10).

### Terpenes

Terpenes are highly lipophilic, aliphatic compounds found in essential oils that are on the FDA's generally regarded as safe (GRAS) list. They disrupt the SC lipid organization (10).

### Fatty Acids

The penetration-enhancing effect of fatty acids also depends on their nature, unsaturated fatty acids being more efficient enhancers than saturated ones and additional double bonds increasing enhancing efficiency further by causing kinks in

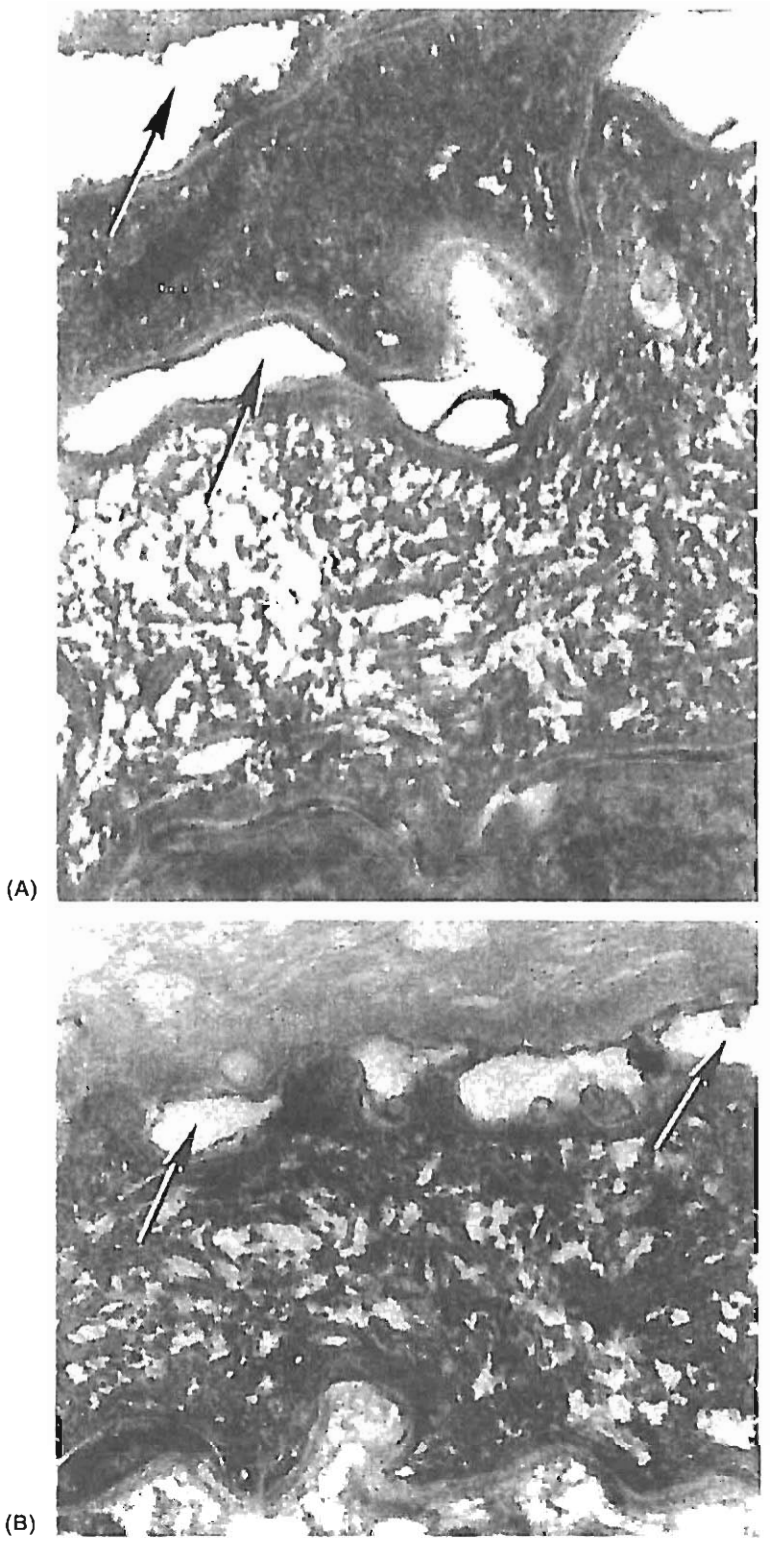



**FIGURE 4** (**A**) Transmission electron micrograph of human stratum corneum after exposure to acetone showing lipid extraction in the upper layers of stratum corneum (*arrows*) but with the intercellular lamellar being largely intact in the lower layers (×32,000). (**B**) Transmission electron micrograph of human stratum corneum after exposure to ethanol showing a similar lipid extraction effect (*arrows*) as seen for acetone (×32,000).

the intercellular lipid tail structure (10). For saturated fatty acids, a 10- or 12-carbon alkyl chain linked to a polar group is an optimal enhancer whereas, for unsaturated alkyl chains, an 18-carbon chain length is preferred. A bent *cis* configuration also has a higher likelihood of disturb the bilayer lipids organization (10). A synergistic mechanism has been observed between oleic acid and benzyl alcohol, the polar penetration route was increased probably by interaction with polar and nonpolar SC lipids (10).

### Hydrocarbons

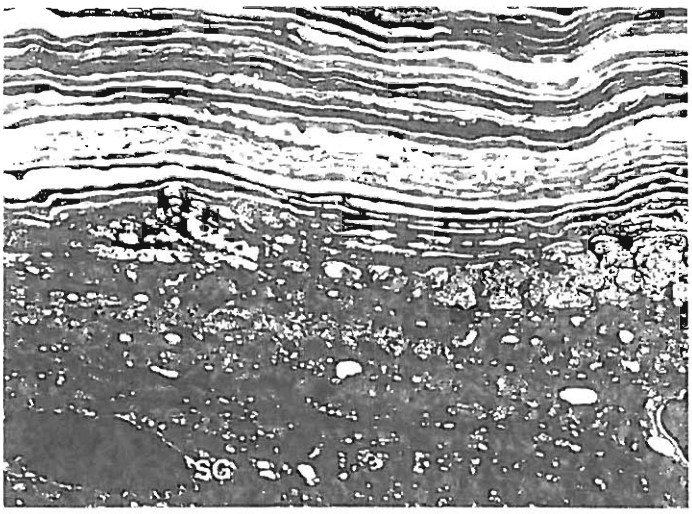
Hydrocarbons are usually classified as being either low or high in MW. High-MW hydrocarbons (e.g., petroleum jelly) are occlusive. Naturally anhydrous, petroleum jelly moisturizers can reduce water loss by more than 98%, when compared with many other oils which lead to 20% to 30% reduction. Petroleum jelly also can diffuse into the intercellular lipid domain (13).

Exposure to hydrocarbons can markedly disrupt the SC (1). As discussed earlier, Figure 3A shows that focal areas of lipid lamellae detachment occurs after exposure to cyclohexane whereas Figure 3B shows that focal areas lacking lipid are evident within the intercellular spaces of the SC following the application of a mixture of cyclohexane and ethanol in a 4:1 ratio. Focal areas lacking the normal compact lipid lamellae within the intercellular lipid bilayers of the SC were noted. Many other methods were used to extract lipids from the abdominal, inguinal, and back regions of the pig. In general, the mean total lipid concentration depended on the extraction solvents and body region, and was reproducible across different sites. This study had demonstrated that extraction of lipids increased the transepidermal water loss similar to repeated tape stripping. In addition, it suggested strategies that could alter the lipid composition that could increase the absorption of topical compounds for enhanced drug delivery (14).

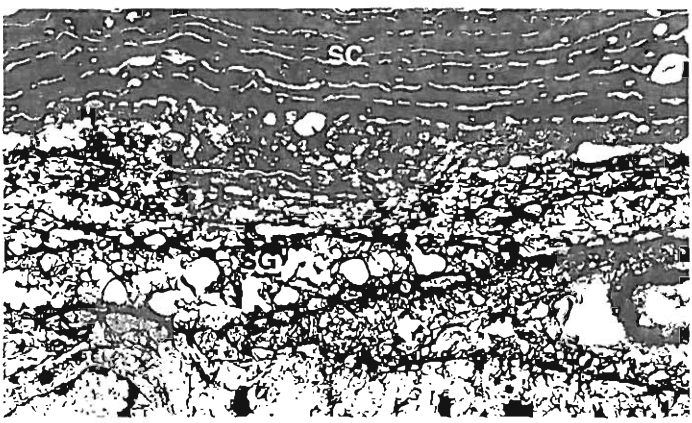
JP-8 jet fuel is mostly composed of aliphatic and aromatic hydrocarbons. Topical application of hydrocarbons were applied to in vivo pigs after one day and after repeated exposures for four days and then removed on the fifth day. Figure 5B,C shows both light and electron micrographs of skin from the back of the pig after repetitive treatments with different jet fuels, Jet A, JP-8, and JP-8 + 100. After four days of repeated application a disorganized stratum granulosum (SG)–SC interface with loosely packed filaments, numerous lacunae, and remnants of keratohyalin granules can be observed, relative to control (Fig. 5A). Repetitive treatments with jet fuels by electron microscopy showed focal areas of vacuoles devoid of lipid within the intercellular space of the SG layers. All jet fuels, especially JP-8 + 100, showed cleft formations within the intercellular lipid lamellar bilayers (Fig. 5C) (2).

Ultrastructural studies of ruthenium tetroxide staining of the lipid bilayers between the SC layers after one day of exposure to aliphatic and aromatic hydrocarbons revealed large lacunae resulting from lipid extraction in the SC intercellular lipid layers after exposure to fabric soaked in JP-8 (Fig. 6B), fabric soaked in *o*-xylene (Fig. 6C), and fabric soaked in tetradecane (Fig. 6D), relative to control (Fig. 6A) (15).

Ultrastructural observations after treatment of skin with both aromatic and aliphatic hydrocarbons for four days and evaluated on the fifth day caused similar damages to the SC lipid bilayers, but the intensity of damaged was enhanced with prolonged exposure to the aromatic and aliphatic hydrocarbons (Fig. 7B,C,D) compared to control (Fig. 7A) (15).




(A)

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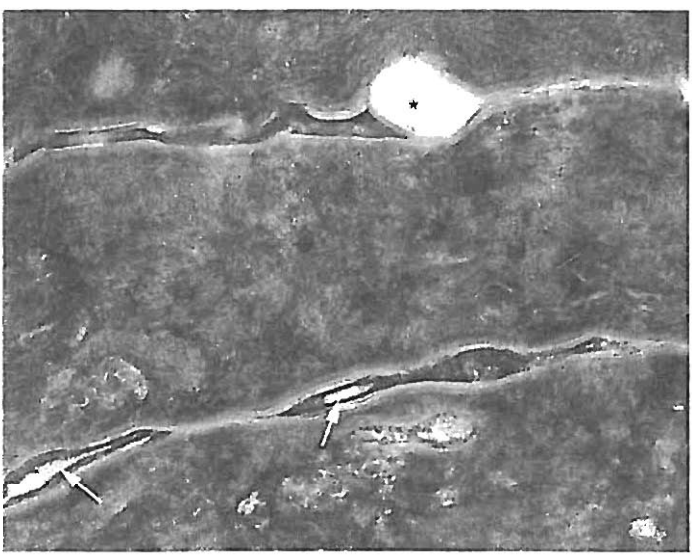


(C)

**FIGURE 5** Effect of jet fuels on pig skin histology. (**A**) Normal skin, showing SC and SG with normal electron-dense keratohyalin granules and tightly packed filaments (×9600) and (**B**) repeated application over four days showing the loosely packed filaments in the SG (×7500). (**C**) Transmission electron microscopy of the SC layers following repeated application over four days (×117,000). White arrows and astrick depict vacuoles devoid of lipid. White arrow depicts desmosome separation from the central co... *Abbreviations*: D, desmosomes; SC, stratum corneum; SG, stratum granulosum. *Source*: From Ref. 2.

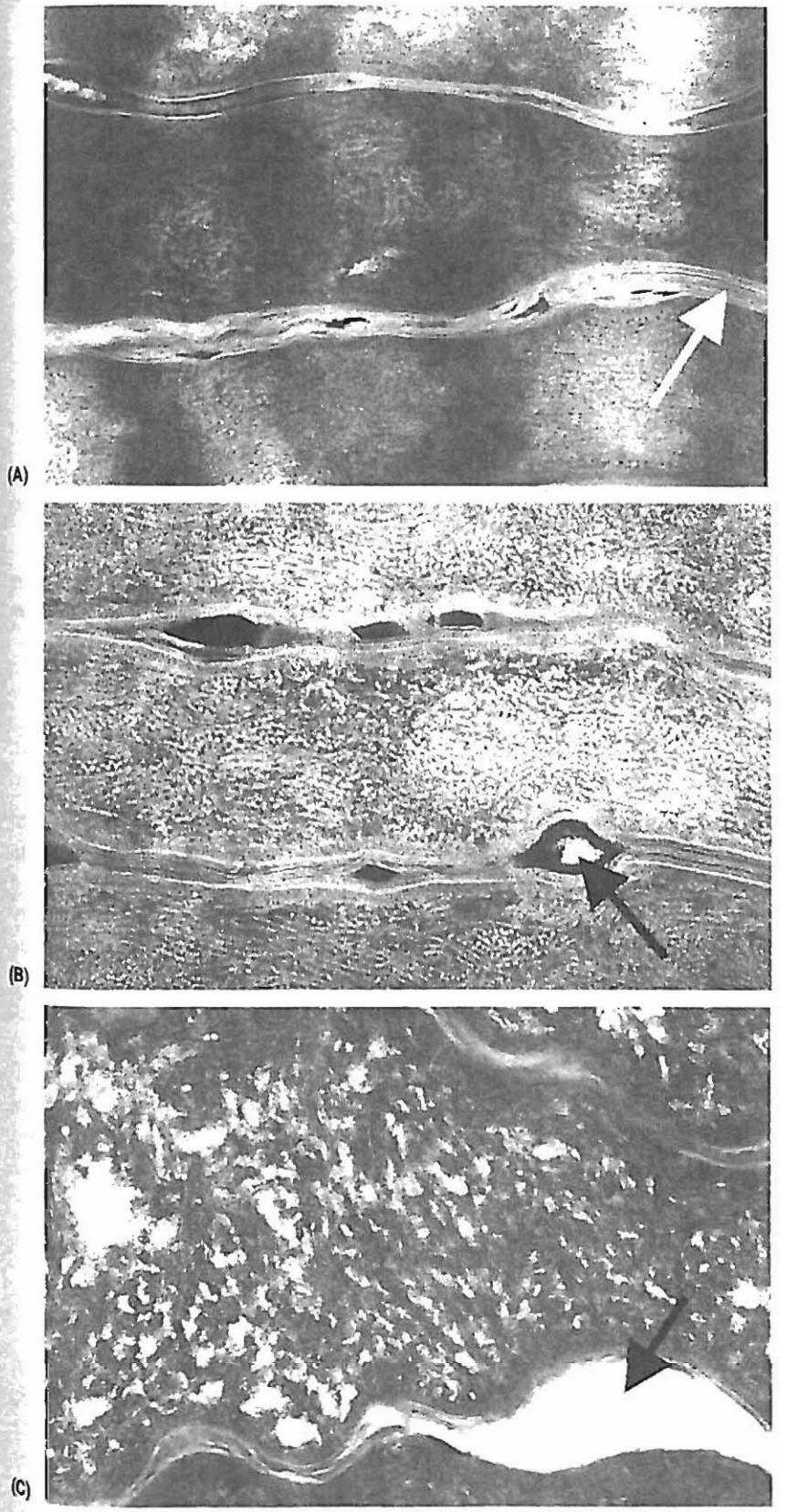
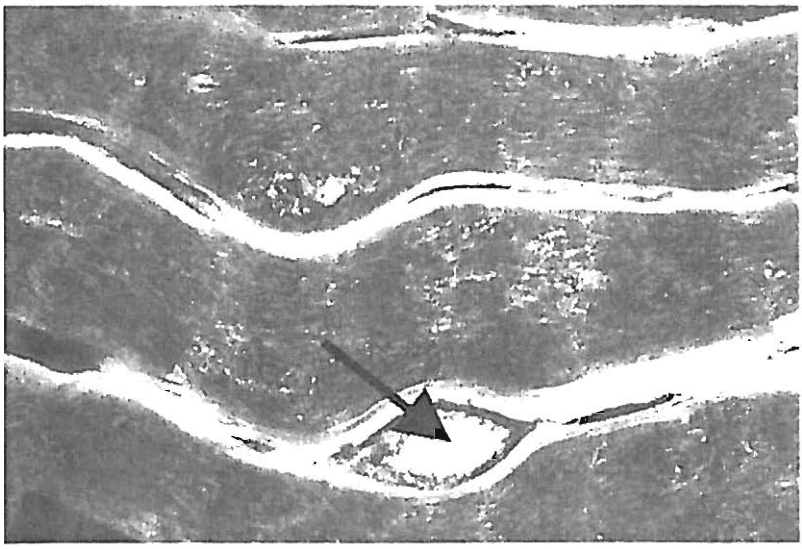



**FIGURE 6** Transmission electron micrographs of the stratum corneum cell layers following one-day exposure to (**A**) control fabric, (**B**) fabric soaked in JP-8, (**C**) fabric soaked in *o*-xylene. *Source*: From Ref. 15. (*Continued*)



(D)

**FIGURE 6** (*Continued*) (**D**) fabric soaked in tetradecane. Note the intact lipid bilayers (*white arrow*) and expanded intercellular spaces (*black arrows*) where the intercellular lipid lamellae appeared extracted (×70,000, ruthenium tetroxide staining). *Source*: From Ref. 15.

### Cutting Fluids

Cutting fluids are either oil–water mixtures or strictly synthetic aqueous formulations, they are used in the metal machine industry when cutting metal in order to lubricate and reduce heat generation. Aqueous cutting fluids usually include a surfactant (e.g., linear alkylbenzene sulfonate), a biocide (e.g., triazine, TRI), a fatty acid performance lubricant (e.g., sulfurized ricinoleic acid), and a corrosive inhibitor (e.g., triethanolamine, TEA). In order to simulate both types of cutting fluids, the compounds were formulated in either mineral oil or polyethylene glycol 200 to mimic this exposure. They are usually alkaline and soap like, thereby can denature keratin and extract lipids and water from the skin (16). Figure 8A and B depicts dermal inflammation, intracellular epidermal edema, and epidermal infiltrates observed after treatment with lubrication oils. Dermal edema and dermal inflammation were pronounced with TEA and TRI.

## QUANTITATING SOLVENT INTERACTIONS WITH THE SKIN

Quantitative structure permeability relationships are often used to describe chemical absorption across membranes including the skin (17–19). The form of these equations, based on linear solvation or free energy relationships (LSER, LFER), involves defining a multiple regression equation linking the parameter of interest, say membrane permeability ($K_p$) to a number of molecular descriptors ($A,B,C\ldots$) (e.g., hydrogen bonding, molecular size, solubility, polarizability, etc.) via strength coefficients ($a,b,c\ldots$) that relate the parameter of interest to the solute molecular properties. The general form of such equations is thus

$$K_p = \text{Intercept} + aA + bB + cC\ldots$$

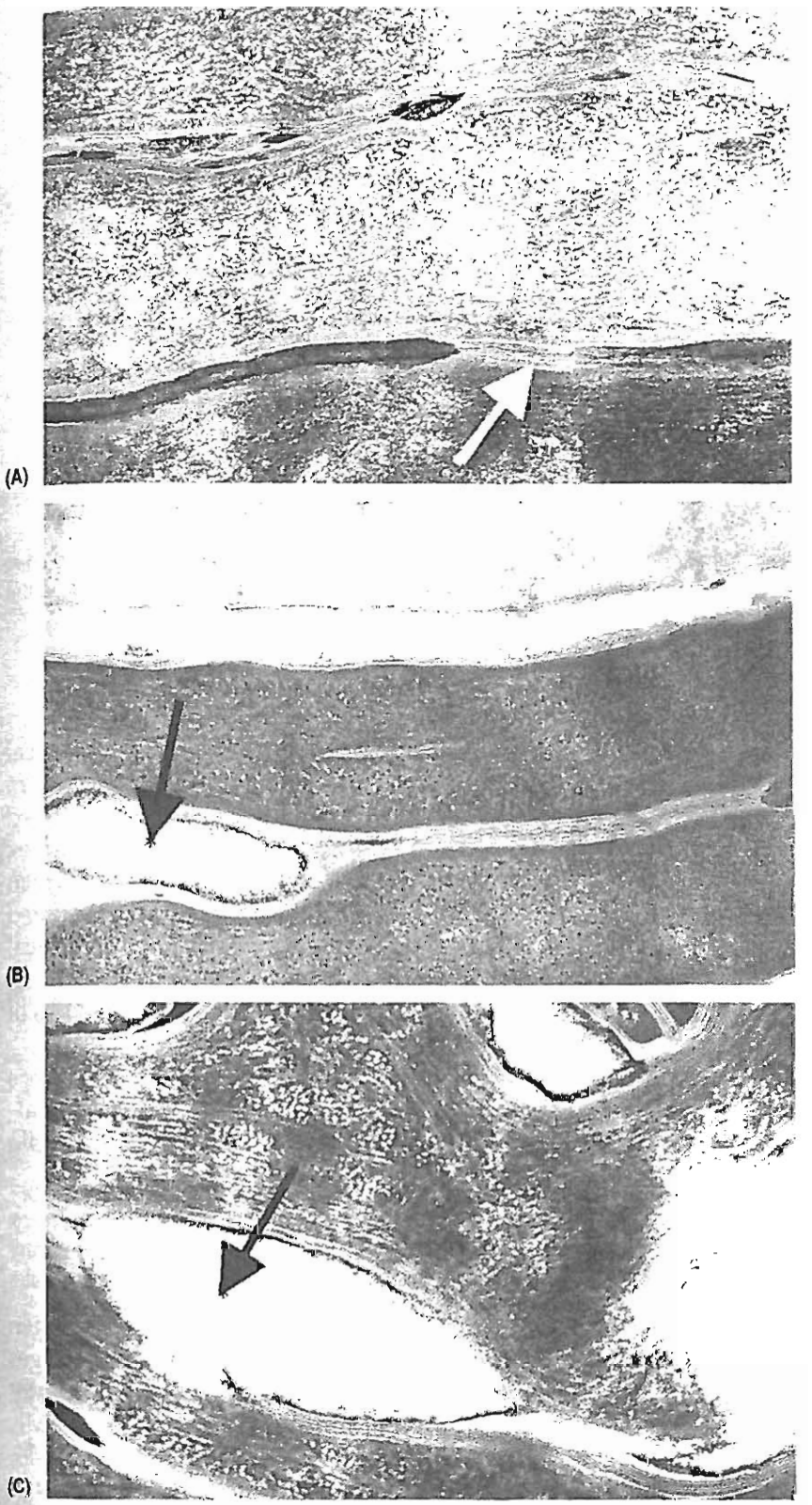



**FIGURE 7** Transmission electron micrographs after ruthenium tetroxide staining of the lipid bilayers between the stratum corneum cell layers following four-day of exposures to (**A**) control fabric, (**B**) fabric soaked in JP-8, (**C**) fabric soaked in *o*-xylene. *Source*: From Ref. 15. (*Continued*)

(D)

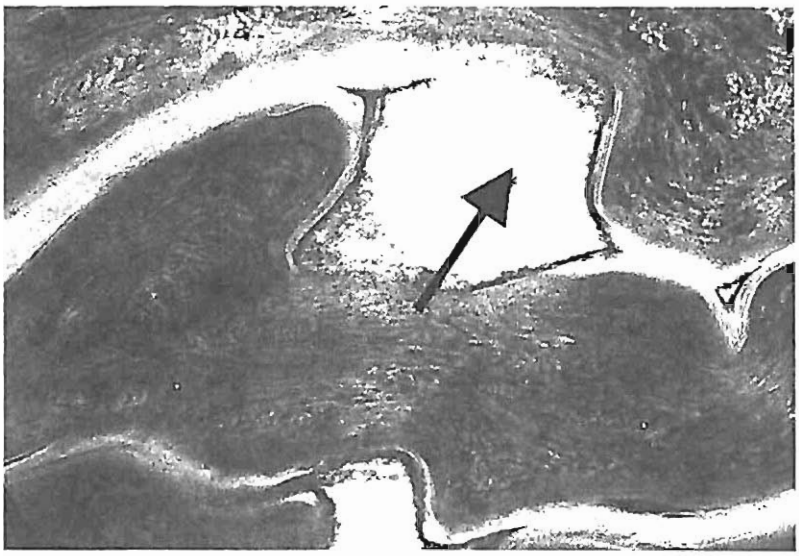


**FIGURE 7** (*Continued*) (**D**) fabric soaked in tetradecane. Note the intact lipid bilayers (*white arrow*) in control, and expanded intercellular spaces (*black arrow*) in treated samples where the intercellular lipid lamellae were extracted (×70,000). *Source*: From Ref. 15.

The data used to define such relationships are obtained from chemical exposure in water. These types of relationships have found wide applicability in many fields. However, under normal exposure conditions say for skin, as discussed earlier exposure to chemicals most often occurs in solvents or other complex mixtures which may modulate the intermolecular interactions seen between solute–solvent–membrane (skin) that define the LSER equation. This has prohibited use of equations defined in aqueous systems to be used to predict chemical absorption from other solvents or vehicles. In many cases, solvent effects on penetrant penetration can be correlated to specific physical–chemical properties of the solvent (19).

An approach to compensate for these solvent–solute–membrane interactions is to add another term to the basic LSER model that takes into account the physical–chemical nature of these interactions (20,22). This could be incorporated as a mixture factor (MF) as

$$K_p = \text{Intercept} + m\text{MF} + aA + bB + cC\ldots$$

where the MF is a physical–chemical property of the vehicle (e.g., hydrogen bonding, Henry's constant, ovality) calculated based on the weight percentages of the vehicle components. The parameter selected is that which significantly improves the predictability ($R^2$, $Q^2$) of the base equation over that without a MF, determined by correlating the vehicle component weighted MF to the residual plot of the original equation (Fig. 9). This approach has worked for different forms of LFER across two skin model systems (diffusion cells, isolated perfused skin flap). In addition to this approach illustrating the impact the vehicle effect has on chemical dermal absorption, it also provides a method to quantitate this effect using available chemical properties of specific solute and solvent combinations.

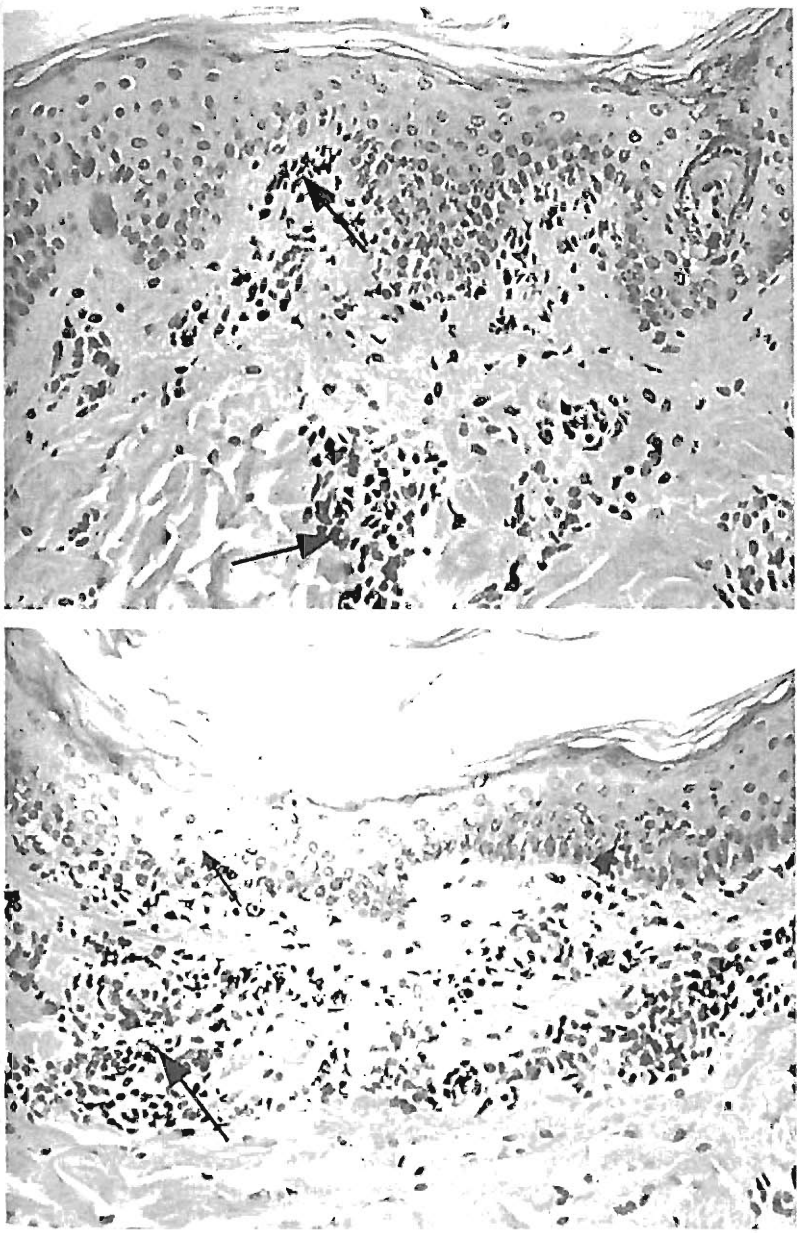



**FIGURE 8** (**A**) Light micrograph of porcine skin treated with 5% linear alkyl benzene sulfonate, 5% triethanolamine, and 2% triazine for eight hours depicting dermal inflammation (*arrows*). (**B**) depicts intracellular epidermal edema (*small arrow*), epidermal infiltrates (*arrow head*), and dermal inflammation (*large arrow*). (Hematoxylin and eosin, ×175.)

## CONCLUSION

Most solvents affect the SC, but to what extent depend on their ability to enter the skin and interact with lipid and protein components in both the intercellular and the cellular regions. But the nature of the interactions between the solvents and the epidermal components are numerous. In addition, solvents can be chemically transformed by enzymes present in the skin, resulting in either detoxification or in generation of toxic derivatives of what was previously an inert compound (23).

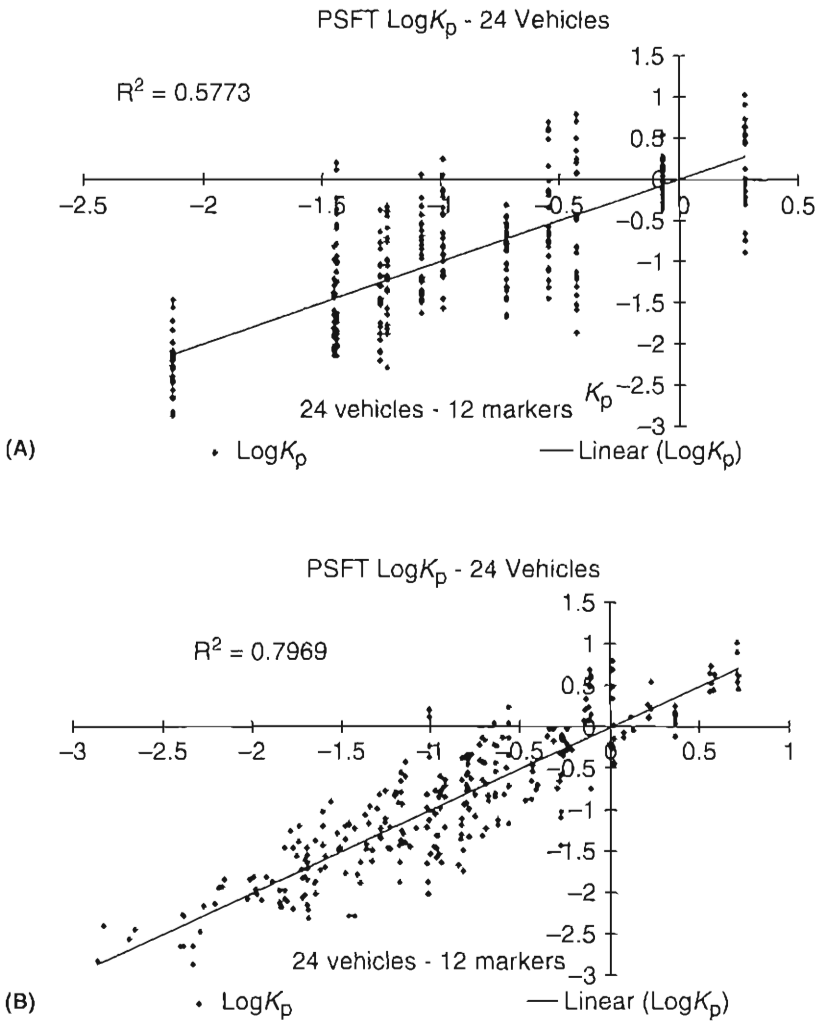



**FIGURE 9** Illustration of the effect of a mixture factor on improving quantitative structure permeability relationship prediction of chemical dermal absorption of 12 compounds in 24 vehicles in porcine skin flow-through diffusion cells. (**A**) No mixture factor and (**B**) mixture factor equal to 1/(vapor pressure) of weighted vehicle components. *Abbreviation*: PSFT, porcine skin flow-through.

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# Dermal Absorption and Toxicity Assessment

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Edited by

**Michael S. Roberts**

*School of Medicine, University of Queensland*
*Princess Alexandra Hospital*
*Buranda, Australia*

**Kenneth A. Walters**

*An-eX Analytical Services Ltd.*
*Cardiff, United Kingdom*

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