DERMAL ABSORPTION AND PHARMACOKINETICS OF ISOPROPANOL IN THE MALE AND FEMALE F-344 RAT

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ABSTRACT:

Isopropanol (IPA), as a 70% aqueous solution, was applied under occluded conditions to the shaved backs of male and female Fischer F-344 rats for a period of 4 hr. Maximum analyzed blood concentrations of IPA were attained at 4 hr and decreased steadily following removal of the test material. Blood concentrations were below the limit of quantification at 8 hr. Acetone (ACE) blood levels rose steadily during the 4-hr exposures and continued to rise following removal of the test material, reaching peak analyzed levels at 4.5 hr (male) and 5 hr (females). ACE blood concentrations were below the limit of quantitation at 24 hr. Basic pharmacokinetic parameters were similar for male and female rats with mean, first-order elimination half-lives for IPA and ACE of 0.8 to 0.9 hr and 2.1 to 2.2 hr, respectively.

Following iv administration of \(^{14}\text{C}\)IPA, 50–55% of the dose was eliminated as \(^{14}\text{CO}_2\) with lesser amounts recovered as expired volatiles or in urine. Total recoveries following iv administration were 83% for both males and females. Following a 4-hr dermal exposure to \(^{14}\text{C}\)IPA (70% aqueous solution), 84–86% of the dose was recovered from the application site. Dermal absorption rates were calculated by two independent methods. The values obtained were 0.78 ± 0.03 and 0.85 ± 0.04 mg/cm\(^2\)/hr for males and 0.77 ± 0.13 and 0.78 ± 0.16 mg/cm\(^2\)/hr for females. Calculated permeability coefficients of 1.37 to 1.50 x 10\(^{-3}\) cm/hr for males and 1.35 to 1.37 x 10\(^{-3}\) cm/hr for females indicate that in the rat, IPA is rapidly absorbed dermally when applied under occluded conditions.

IPA\(^1\) is used as a solvent, as a component of numerous industrial and consumer products, and in the production of acetone and acetone derivatives (Lington and Bevan, 1994). Human exposure to IPA may occur through the manufacture and distribution of this material as well as from direct exposure to a variety of consumer products including rubbing alcohol, skin lotions, aerosol products, and deicing and anti-freeze solutions (U.S. Environmental Protection Agency, 1989). Reported adverse health effects in humans resulting from the current routine manufacture processes and from the use of IPA are limited to a few cases of either dermal irritation or sensitization. Poisonings as a result of intentional ingestion of IPA normally result in a comatose condition with typical signs or symptoms including pulmonary difficulty, nausea, vomiting, headache, and central nervous system depression. Intoxications as a result of sponge bath treatments for the control of fever have also produced comatose conditions with recoveries in all cases within 34 hr (Lington and Bevan, 1994).

In animals and humans, IPA is metabolized primarily to ACE by hepatic alcohol dehydrogenase. Expired air is the major route of excretion following inhalation, oral, iv, or ip exposures. In animals, the elimination of IPA from blood is a first-order process at oral doses less than 1500 mg/kg (Lington and Bevan, 1994). A recent report by Slauder et al. (1994) of the disposition and pharmacokinetics of \(^{14}\text{C}\)IPA in male and female rats and mice following iv, inhalation, or oral exposures indicates a rapid elimination of label in the expired air (as ACE, \(^{14}\text{CO}_2\), and IPA). In this latter study, rates and routes of excretion were similar regardless of sex or route of administration. The first-order elimination half-lives for IPA in these studies ranged from 1 to 2 hr and were found to increase with increasing dose for both rats and mice. In humans, first-order half-lives of 0.8 to 16 hr have been reported for the elimination of IPA (Lington and Bevan, 1994; Monaghan et al., 1995).

The early literature would suggest that IPA is poorly absorbed through the skin, resulting in negligible toxicity (Grant, 1923; Bough- ton, 1944). Thus, reports of deep coma in pediatric cases resulting from the use of isopropanol sponge bath treatments for fever reduction were attributed to inhalation exposure (Martinez et al., 1986). More recent work by Martinez et al. (1986) in rabbits indicates that dermal absorption of IPA may contribute significantly to the toxicity of this material and that the delayed rise in blood acetone levels following dermal exposure may be responsible for the prolongation of the toxic effects. These workers report IPA blood concentrations in rabbits as high as 112 mg/dl following 4-hr combined dermal and inhalation exposures, with control studies indicating that inhalation exposure alone contributed little to the observed blood levels. Neither total dose absorbed nor absorption rate data were reported by these workers. The current studies were undertaken to determine the disposition and pharmacokinetics of \(^{14}\text{C}\)IPA following occluded dermal exposure in male and female rats. In

\(^{1}\) Abbreviations used are: IPA, isopropanol; ACE, acetone; GC/MS, gas chromatography/mass spectrometry; GC/FID, gas chromatography/flame ionization detection; LSS, liquid scintillation spectrophotometry.

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vivo dermal absorption rates for IPA were calculated by a comparison of recoveries of radiolabel between iv and dermal exposures.

Materials and Methods

Test Materials and Dosing Solutions. IPA (2-propanol, CAS No. 67-63-0) was obtained from Fisher Scientific. Analysis by GC/MS confirmed the structure and indicated a purity in excess of 99%. Radiolabeled IPA (2-propanol-2-14C, [14C]IPA) was obtained from Sigma as a solution in isotonic saline. The radiochemical purity of the [14C]IPA as determined by high pressure liquid chromatography with radiochemical flow detection was in excess of 99%. Structural confirmation of the [14C]IPA was obtained by GC/MS. The concentration of IPA in dosing solutions was determined by GC/FID on the day prior to use and immediately following dosing to confirm the concentrations and stabilities of the dosing solutions. All other chemicals were of reagent grade purity unless otherwise noted.

Animals. Male and female Fischer F-344 rats [CDF/F-344/Crl Br] were obtained from Charles River Kingston (Stone Ridge, NY) and were from 10 to 12 weeks of age at the time of use. Animal body weights at the time of dosing ranged from 219 g to 246 g for male rats and 140 g to 163 g for female rats.

Dose Formulations. Dosing solutions used for dermal applications were 70% (by weight) IPA. For radiochemical dosing preparations, sufficient concentrations and stabilities of the dosing solutions. All other chemicals were of reagent grade purity unless otherwise noted.

Dermal Exposure Chambers. The hair from all test animals was clipped from the thoracic region immediately prior to the interscapular area of each animal approximately 24 hr prior to dose application. All animals were examined prior to dosing, and any appearing in poor condition or having abraded skin were not used in the study. On the morning of each study, chambers fabricated from 3.18-cm-diameter (external) borosilicate glass tubing were attached to the test animals using a continuous bead of Permatbond 910 (Pemabond International Division, Englewood, NJ) cyanoacrylate glue (Boatman et al., 1993). A circular piece of polyethylene sheet stock (0.8-mm thickness) was glued to the top of each chamber as a cover. The surface area of skin enclosed by the cells was 4.3 cm2, and the aqueous test solution was observed to completely wet the surface of the skin.

Administration of Test Chemical. IPA was administered iv as a bolus injection (0.25 ml) into a lateral tail vein using a 1.5-gauge needle equipped with a 26-gauge needle. In the case of iv dosing, a fixed amount of IPA (6 mg/rat) was administered to each animal to approximate the situation to result following dermal applications. Aqueous IPA solutions (0.3 ml) were delivered by syringe to the dermal exposure chambers through a small hole bored in the cover of each chamber. These holes were covered immediately with a small piece of polyethylene material glued in place with Permatbond 910. Syringe weights were recorded before and after each dose application to determine the weight of administered dose. Using this procedure, male rats received a mean dermally applied dose of 0.1800 g of IPA and female rats a dose of 0.1762 g of IPA.

Dermal Blood-Kinetics Study. Aqueous IPA was administered to a total of eight test animals (four of each sex). Excess test material was removed at 4 hr, and the dermal exposure sites were washed repeatedly with distilled, deionized water (5 × 1 ml) and dried using cotton swabs. All cells contained residual test material at 4 hr, and no leakage was apparent. Blood was sampled at 30 min and at 1, 2, and 4 hr during the 4-hr exposure period and at 4.5, 5, 6, 8, and 24 hr (after completion of dosing).

Disposition Studies Following Iv or Dermal Administration of [14C]IPA. Groups of three male or female rats were administered [14C]IPA iv in isotonic saline at a nominal concentration of 24 mg/g (6 mg/rat). Alternatively, similarly-sized groups of rats were dosed dermally with [14C]IPA (0.3 ml/rat) as described for the dermal blood-kinetics study. All dosed rats were placed immediately into individual, all-glass metabolism chambers (Metabowl, Jencons Ltd., Hemel Hempstead, Herts, England). After 4 hr, rats receiving the dermal dose were removed briefly from the chambers, unabsorbed liquid at the exposure sites was rapidly recovered, and the sites were washed repeatedly with distilled, deionized water (5 × 1 ml) and dried with cotton swabs. All washings and swabs (as well as the plastic covers from the exposure chambers) were saved for subsequent radioactivity analysis by LSS. Following recovery of the residual dose, animals were immediately returned to the metabolism chambers for the duration of the study. Urine and cage wash samples, expired volatile organics (trapped with silica gel), and expired CO2 (trapped in 2.5 M sodium hydroxide) were collected at 8, 24, and 48 hr following dose administration and analyzed for radioactivity by LSS. Feces were collected at 24 and 48 hr and were homogenized with deionized, distilled water. An aliquot of this mixture was combusted (Packard Model 306 Sample Oxidizer, Packard Instruments Company, Downers Grove, IL) and analyzed for radioactivity by LSS.

Washing Efficiency Studies with [14C]IPA. Groups of three male or female rats were administered [14C]IPA dermally as described above for the disposition studies. After approximately 5 min, the dose was removed from the chambers, and unabsorbed liquid at the exposure sites was recovered. Animals were then returned into all-glass metabolism chambers, and urine and cage wash samples, expired volatile organics, expired CO2, and feces were collected and analyzed for a period of 24 hr following administration of the dose.

Blood Analyses. Blood was sampled by retro-orbital sinus puncture (approximately 0.2 ml) or was collected at study termination (24 hr) by exanguination after the posterior vena cava. Blood samples were kept on ice or were refrigerated prior to analysis. All blood samples were processed on the day of collection by a modification of the method of Smith (1984). Processing consisted of a brief centrifugation (1000g, 5 min, 5°C) to separate plasma. Weighed plasma samples (approximately 50 mg) were prepared by mixing with 50 μl each of 0.2 M sodium tungstate, 0.2 M cupric sulfate, and an internal standard solution (1 mM n-propanol) and were briefly centrifuged (16,000g, 5 min, 5°C); a second time to remove precipitated plasma protein. The clear supernatants from this procedure were analyzed by GC/MS using an adaptation of the methods of Smith (1984) and of Chueng and Lin (1987) to quantitate levels of acetone and isopropanol. Standards were prepared by spiking whole blood from a control animal with known amounts of ACE and IPA; these standards were processed in the same manner as were test samples. As a result, analyzed concentrations of IPA and ACE in plasma could be directly related to concentrations in whole blood. Treated plasma samples were analyzed by GC/MS using the following conditions: instrument, Hewlett-Packard 5890 GC with 5970 MSD; column, DB-1701 (J & W Scientific, Folsom, CA), 30 M × 0.25 mm (0.2-mm film thickness); head pressure, 5 psi; oven, 30°C (isothermal, 6-min run time); injector, split (flow = 30 ml/min); injection temperature, 280°C; injection volume, 1 μl; mode (MSD), single ion monitoring (ions: 43.10, 45.10, and 31.10 AMU). Figure 1 contains representative chromatograms.

Calculation of Pharmacokinetic Parameters. A linear equation of the form shown in eq. 1 was fitted to the mean analyzed concentrations of IPA iv in male and female rat blood obtained during the 4-hr dermal exposures.

\[ C_t = m \cdot t + b \]  (1)

In eq. 1, \( C_t \) is the blood concentration of IPA at time \( t \) (see fig. 4).

A mono-exponential equation of the form shown in eq. 2 was fitted to the mean IPA blood concentrations from the 4-, 4.5-, and 5-hr sampling times for male rats or from the 4-, 4.5-, 5-, and 6-hr sampling times for female rats following the 4-hr dermal exposures (see fig. 5).

\[ C_t = A_1 \cdot e^{-k_1 t} + A_2 \cdot e^{-k_2 t} \]  (2)

In eq. 2, \( k_1 \) is the first-order elimination rate constant. The half-life of IPA was calculated as shown in eq. 3.

\[ T_{1/2} = \frac{k_1}{0.693} \]  (3)

A di-exponential function of the form shown in eq. 4 was fitted to the mean analyzed concentrations of ACE in male and female rat blood following dermal exposures.

\[ C_t = A_1 \cdot e^{-k_1 t} - A_2 \cdot e^{-k_2 t} \]  (4)

In eq. 4, \( C_t \) represents the measured blood concentration of ACE in male and female rats from 4 hr (end of dermal exposures) to 8 hr. The terminal elimination rate constant for ACE is represented by the term \( k_2 \). The terminal half-life of ACE in rat blood was calculated from \( k_2 \) according to eq. 3.

Calculation of Dermal Absorption Rates. Two methods were used to calculate the in vivo rate of dermal absorption of [14C]-IPA in rats. In the first method, total recovered radioactivity following an iv administration was ap-
plied as a normalization factor to recoveries following dermal administration. Thus, following dermal exposures to [14C]IPA, the amount of absorbed radioactivity was assumed to equal the total radioactivity recovered from urine, feces, chamber rinses, expired 14CO₂, and volatile organics. These total recovery values were corrected to 100% by dividing the total by the fraction of administered radioactivity recovered following iv administration. Alternatively, expired 14CO₂ (from NaOH traps) following iv administration was used as a dosimeter for absorbed radioactivity. In this procedure, total radioactivity as expired 14CO₂ following dermal administration was corrected to 100% by dividing the total by the fraction of radioactivity recovered as 14CO₂ following iv administration.

In the case of male rats, an absorption rate (mg/cm²/hr) for IPA was calculated as shown in the following example (calculation based on total recovered radioactivity):

% absorbed dose (table 3) \[= 91.20\% \] (total recovered) / \[= 84.43\% \] (recovered dose) = 6.77%. Corrected recovered dose = 6.77% \[\times 0.8311\] (table 2) = 8.15%. Thus, mg IPA absorbed/hr = [180.0 mg (administered IPA) \[\times 0.0815\] \[\div 4\] hr] = 3.66 mg IPA/hr. Absorption rate (mg/cm²/hr) = 3.66 mg IPA/hr \[\div 4.3\] cm² = 0.85 mg/cm²/hr (table 4).

Absorption rates for female rats were calculated similarly. Permeability coefficients (K_p) were derived from the absorption rates by dividing by the concentration of IPA in the administered aqueous solution (568.5 mg IPA/g solution).

Regression and Statistical Analyses. The program SAS/STAT (Version 6.02, SAS Institute, Inc., Cary, NC) was used to perform all regression analyses and statistical comparisons. Unless otherwise stated, all results represent the mean ± 1 SD for either three or four animals. The asymptotic standard errors for fitted parameters are reported. IPA and ACE blood concentrations were analyzed for both gender-related and time-related statistical differences. If necessary, data were transformed into ranks for nonparametric analyses. An appropriate repeated measures’ analysis of variance model was used to detect significant differences (α level of 0.05).

Results and Discussion

Dermal Blood-Kinetics Study. Mean concentrations of IPA and ACE in blood from male and female F-344 rats are summarized in figs. 2 and 3. Concentrations of IPA reached quantifiable levels by 1 hr and increased steadily through 4 hr, reaching maximum concentrations of 0.19 μmol/g (for males) and 0.24 μmol/g (for females) at 4 hr. Concentrations of ACE reached quantifiable levels by 30 min and continued to rise during the 4-hr exposure period reaching concentrations of 0.67 μmol/g (for males) and 0.78 μmol/g (for females) at 4 hr. ACE concentrations continued to rise subsequent to exposure, attaining significantly (p < 0.05) higher observed peak levels in females vs. males at the 5-, 6-, and 8-hr sampling points. IPA concentrations fell below quantifiable levels at the 6-hr sampling time for males and at the 8-hr sampling time for females. Mean measured concentrations of IPA for male and female rats did not significantly differ at any measured time point (p ≤ 0.05). The concentration of ACE in blood had fallen to a level of 0.30 μmol/g (for males) and 0.55 μmol/g (for females) at 8 hr and was not quantifiable by 24 hr.

Summarized in table 1 are calculated first-order elimination rate
Constants and half-lives for IPA and ACE in rat blood. For IPA, the elimination rate constants were 0.90 hr\(^{-1}\) and 0.74 hr\(^{-1}\), respectively, for male and female rats. These values correspond to half-lives for IPA in blood of 0.77 hr and 0.93 hr, respectively. For ACE, the terminal elimination rate constants were 0.32 hr\(^{-1}\) and 0.33 hr\(^{-1}\), respectively, for male and female rats. These values correspond to half-lives for ACE in blood of 2.2 hr and 2.1 hr, respectively.

IPA blood concentrations were found to increase linearly over the 4-hr exposures with no apparent approach to an equilibrium or plateau value (fig. 4). This result is surprising in view of the rapid elimination half-life (<1 hr) for this material in the rat (Slauter et al., 1994). Based on an assumption of simple first-order elimination from a single compartment, such rapid elimination would suggest that IPA blood concentrations should have approached an equilibrium or plateau value by 2.5 to 3 hr. The current experimental findings can be explained if the absorption rate is assumed to increase during the 4-hr exposures. The most likely cause of this increasing rate of absorption is an increase in the hydration state of the stratum corneum. Such hydration does occur slowly over the course of 2 to 3 days with human skin in vitro (Scheulplein and Morgan, 1967). In this respect, the epidermis or stratum corneum has been shown to be the principle barrier to penetration of alcohols in human skin (Scheulplein and Blank, 1973). Scheulplein (1964) reports that measured in vitro values of \(k_p\) for n-pentanol increase by a factor of approximately 2 over a period of 3 days after exposure to a dilute aqueous solution of the alcohol. It is proposed that hydration results in the creation of “pores” or “holes” in the stratum corneum through which increased absorption occurs. Occlusion has also been shown to greatly increase dermal absorption rates by increasing the hydration state of the skin. This has been demonstrated after topical steroid applications and can result in increased fluxes of 10- to 100-fold with occlusion (Vickers, 1963). Alternatively, the alcohol itself may contribute to the increased permeability. This latter possibility has been demonstrated with a series of drug compounds tested in vitro with human skin using either an aqueous buffer or a 1:1 (v:v) mixture of ethanol and water as the receptor solutions (Kasting et al., 1987). Ethanol increased the average rates of penetration by a factor of 1.7 in this system.

Following the removal of excess test material at 4 hr, loss of IPA from blood proceeded rapidly with similar elimination rates calculated for male and female rats (see fig. 5 and table 1). The results from the current studies agree well with similar published data from studies in animals and humans. For example, Slauter et al. (1994) report half-lives for IPA in male and female F-344 rats ranging generally from 1 to 2 hr following iv, oral, or inhalation exposures. These workers report increasing half-lives with increasing doses of IPA, suggesting saturation of the alcohol dehydrogenase enzyme (Lington and Bevan, 1994). Monaghan et al. (1995) report elimination rate constants for IPA in humans ranging from 0.72 to 0.85 hr\(^{-1}\) following oral administration of 70% IPA at a dose of 0.6 ml/kg. Elimination rate constants from this latter study correspond to half-lives of 0.81 to 0.97 hr.

As shown in figs. 2 and 3, ACE concentrations in blood increased steadily during 4-hr dermal exposures to IPA. Peak, measured ACE blood concentrations occurred subsequent to the removal of excess test material at 4 hr, and similar terminal blood elimination half-lives for ACE were obtained for both male and female rats (see fig. 6 and table 1). Plaa et al. (1982) report elimination half-lives for ACE in male Sprague-Dawley rats ranging from 2.4 hr to 7.2 hr following oral administration. Saturation of elimination is apparent at higher doses, resulting in increased half-lives. Monaghan et al. (1995) report elimination rate constants for ACE in humans ranging from 0.035 to 0.048
Results represent mean values for three or four animals, and error bars represent ± 1 SD. Test solutions were applied occluded to a 4.5-cm² area of skin. A di-exponential function was fitted to experimentally determine ACE concentrations at 4 hr (table 3).

Expired CO₂ and volatile organics (IPA for 4 hr). In this regard, Plaa et al. (1994) report CO₂ recoveries of 29 to 30% in male and 1% of recovered radioactivity. A decreased yields of CO₂ in these latter studies are presumably due to the lower body weights of this gender.

Disposition of Radioactivity Following IV Administration of [14C]IPA. Following iv administration of [14C]IPA in rats at a nominal dose of 6 mg/rat, 50 to 55% of the administered dose was eliminated as CO₂ by 48 hr (table 2). Volatile organics accounted for 21 to 26% of the recovered radioactivity in these studies. Small additional amounts of radioactivity were also recovered in urine and corresponded to 6.0% (for males) and 5.1% (for females) of the cumulative total. Cage washes and feces accounted for <1% of recovered radioactivity.

Slauder et al. (1994) report CO₂ recoveries of 29 to 30% in male and female rats following a 300 mg/kg iv dose with combined recoveries of IPA and ACE (expired breath) accounting for the majority of the remainder (54 to 55%). The decreased yields of CO₂ in these latter studies suggest saturation of the metabolic pathways leading from acetone to CO₂. In this regard, Plaa et al. (1982) reported saturation of ACE elimination in rats at blood concentrations in excess of 300 to 400 mg/liter.

Disposition of Radioactivity Following Dermal Administration of [14C]IPA. The majority (84 to 86%) of dermally administered [14C]IPA (70% aqueous solution) was recovered from the dermal exposure sites at 4 hr (table 3). Expired CO₂ and volatile organics accounted for the majority of the additionally recovered radioactivity from these studies with only small amounts found in feces and urine. Total radioactivity recovered following the 4-hr dermal exposures were 91 to 92%. Radioactivity unaccounted for in these studies (8 to 9%) was presumably lost because of volatilization as a consequence of the experimental procedure. This was confirmed in separate dermal studies in which total radioactivity recovered following brief (5-min) exposures indicated losses on the order of 13 to 14% (data not shown).

Dermal Absorption Rates and Permeability Constants for IPA. Summarized in table 4 are the calculated rates of dermal absorption for IPA and the corresponding permeability constants derived from these. Calculated absorption rates based on recovered CO₂ were 0.78 ± 0.03 mg/cm²/hr and 0.77 ± 0.13 mg/cm²/hr for male and female rats, respectively. The corresponding permeability constants based on these values were 1.37 × 10⁻³ (males) and 1.35 × 10⁻³ (females). Similar absorption rate values of 0.85 ± 0.04 mg/cm²/hr and 0.78 ± 0.16 mg/cm²/hr, respectively, for male and female rats were obtained using total recovery of radioactivity as the basis for the calculation. Permeability constants derived from these latter absorption rates were 1.50 × 10⁻³ (males) and 1.37 × 10⁻³ (females). The results from the current studies provide the first measured values for the in vivo permeability of IPA. Similar in vivo results for IPA and most other low molecular weight alcohols are lacking.
However, DiVincenzo and Hamilton (1979) report a dermal absorption rate of 0.53 mg/cm²/hr for n-butanol in the beagle dog when applied as a dilute solution, a result which compares favorably to the values of 0.77 to 0.85 mg/cm²/hr obtained for IPA in the current studies (table 4). Although suitable in vivo results are lacking, it is also appropriate to compare our data with published in vitro results. In this regard, permeability measurements obtained in vitro provide reliable estimates of in vivo values (Barber et al., 1992; Bronaugh et al., 1982a) with differences typically less than a factor of 5 for any specific test chemical. Also, measured differences between in vivo and in vitro results are generally least for water-soluble materials having moderate to rapid rates of dermal absorption (Bronaugh et al., 1982a).

In our studies, permeability values were found to be similar for male and female rats and to compare favorably with published in vitro values for low molecular weight alcohols (table 5). Additionally, although rat skin has been found to be more permeable than human skin in vitro, these differences are generally low (Bronaugh et al., 1982b). In this regard, Morris et al. (1995) report a value of 2.39 × 10⁻³ cm/hr for the permeability coefficient of IPA through full-thickness rat (F-344) skin using 70% aqueous IPA as the test material. These workers also report similar permeabilities for IPA with either full-thickness mouse or human skin (3.37 × 10⁻³ and 3.00 × 10⁻³ cm/hr, respectively).

Summarized in table 5 are a number of permeability coefficients for primary alcohols determined in vitro with human epidermis (Scheulplein and Blank, 1973). IPA results from the current studies agree most closely with those of its isomer, n-propanol. Based on the rating scale developed by Marzulli and co-workers (1969), IPA would receive a skin penetrant rating of “fast” based on the results of these studies.

### Conclusions

Permeability coefficients for IPA through male and female rat skin were calculated in the current studies based on the total absorption of [¹⁴C]IPA over the 4-hr exposure periods. IPA was applied under occluded conditions using a completely sealed exposure chamber to approximate the infinite dose situation in which absorption is limited only by the rate of penetration through the skin. Concentrations of IPA in blood during the 4-hr exposures increased linearly and failed to approach plateau levels, suggesting that absorption was in fact increasing during the 4-hr exposure periods.

Permeability values determined in the current studies should provide an upper limit on the rate of penetration of IPA through human skin. Thus, absorption rates for low molecular weight alcohols measured in vitro through human skin are increased when applied as an aqueous solution (Scheulplein and Blank, 1973). This latter effect has been attributed to increased hydration and swelling of the stratum corneum, thus allowing more rapid penetration of the polar alcohols (Scheulplein and Blank, 1973). In addition, occlusion has been shown to significantly increase the rate of penetration of both methanol and ethanol through full-thickness guinea pig skin in vitro (Gummer and Maibach, 1986). It is anticipated that actual human exposures to IPA under typical use conditions involving brief dermal contact without occlusion would result in total absorbed doses significantly less than those predicted from the current study.

### References


