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IN VITRO HUMAN EPIDERMAL PENETRATION OF 1-BROMOPROPANE

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1-Bromopropane (1-BP; CAS number 106-94-5), also known as *n*-propyl bromide, is a halogenated short-chain alkane used as an organic solvent with numerous commercial and industrial applications, including garment dry cleaning and vapor degreasing of metals. The purpose of this study was to determine the dermal absorption characteristics and corrosivity of 1-BP. Heat-separated human epidermal membranes were mounted on static diffusion cells. Different exposure scenarios were studied (infinite dose, finite dose, and transient exposure) using neat 1-BP and saturated aqueous solution as donor. Steady-state fluxes for infinite-dose neat 1-BP exposure averaged 625 to 960 $\mu g\ cm^{-2}\ h^{-1}$. The finite-dose ($10\ \mu l/cm^2 = 13.5\ mg/cm^2$) unoccluded donor resulted in penetration of <0.2% of the applied dose ($22\ \mu g/cm^2$). A 10-min transient exposure to infinite dose resulted in total penetration of $179\ \mu g/cm^2$. Steady-state 1-BP fluxes from neat application of a commercial dry cleaning solvent were similar (441 to 722 $\mu g\ cm^{-2}\ h^{-1}$). The permeability coefficient of 1-BP in water vehicle was 0.257 ± 0.141 cm/h. The absorption potential of 1-BP following dermal exposure is dependent upon the type and duration of exposure. Donor losses due to evaporation were approximately 500-fold greater than dermal absorption flux; evaporation flux was 420 $mg\ cm^{-2}\ h^{-1}$. 1-BP is cytotoxic but not corrosive, based on results from a cultured reconstructed human epidermal model (EpiDerm Skin Corrosivity Test).

1-Bromopropane (1-BP; CAS number 106-94-5; Table 1), also known as *n*-propyl bromide, is a halogenated short-chain alkane used as an organic solvent with numerous commercial and industrial applications. 1-BP has been identified as an environmentally friendly replacement for ozone-depleting substances (ODS), such as chlorofluorocarbons (CFC), in addition to other substances, such as tetrachloroethylene (also known as perchloroethylene or "PERC"). Common industrial and commercial applications of 1-BP include its use as a substitute for ODS within vapor degreasing and cold cleaning operations of metals and electronic components in the aerospace, military and electronic industries. 1-Bromopropane is also used in adhesive and coatings spray operations during the manufacturing of polyurethane foam cushions (U.S. EPA 2003). In addition, 1-BP is used as an alternative solvent within the dry cleaning industry in response to the restricted use of PERC within certain areas of the United States (Blando et al. 2010; NIOSH 2010). The global demand for 1-BP has increased greatly since the late 1990s in large response to the "green movement," and an estimated 8.2 million lb was used within the United States in 2002 (NTP 2004).

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The findings and conclusions of this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.
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TABLE 1. Some Chemical Properties of 1-Bromopropane (1-BP)

CAS	Formula	Structure	MW	log K_{ow}	VP (mm Hg)	S_W (μg/ml)
106-94-5	C_3H_7Br	Br	123.0	2.10	111	2276

Note. VP: vapor pressure, 20°C; S_W: Water solubility, 32°C (measured herein, mean of three determinations). Source (log K_{ow} and VP): Hazardous Substances Data Bank (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB).

Despite being identified as an environmentally friendly replacement for ODS and PERC, the health effects associated with exposure to 1-BP are poorly characterized. A critical review of human and animal data indicates that 1-BP may be capable of producing a wide spectrum of adverse health outcomes. For example, neurotoxic, reproductive, and hematological effects were documented in workers tasked to produce, handle, or use 1-BP-containing materials (Sclar 1999; NIOSH 2001; 2002a; 2000b; 2003; 2010; Ichihara et al. 2002; 2004a; 2004b; Majersik et al. 2007; Raymond and Ford 2007; Perrone et al. 2008; Li et al. 2010). Similar adverse effects were reported from in vivo animal experiments. The findings of inhalation studies provide evidence of the onset of neurotoxicity, hepatoxicity, hematoxicity, and reproductive and developmental toxicity, in addition to carcinogenicity in rodents following exposure to 1-BP vapors (Kim et al. 1999; Fueta et al. 2000; Ichihara et al. 2000a; 2000b; 2002; Furuhashi et al. 2006; Banu et al. 2007; Liu et al. 2009; NTP 2009). Hepatoxicity and immunotoxicity in rodents treated orally or via intraperitoneal (ip) injections were reported (Lee et al. 2005; 2007; 2010). Overall, 1-BP appears to be a systemic toxicant with a range of adverse effects.

Dermal absorption of organic solvents including tetrachloroethylene is well documented (e.g. Frasch and Barbero 2009). For this reason, during the assessment of health risks associated with organic solvents, it is necessary to identify the potential for dermal penetration and the overall contribution of dermal uptake of a substance to the systemic dose. Unfortunately, currently available data are insufficient to characterize the dermal uptake or systemic toxic effects associated with dermal exposures to 1-BP. Studies of workers exposed to 1-BP-containing materials indicate that the solvent may be absorbed by the skin and contribute to systemic toxicity, but the results of these investigations are confounded by the inhalation of 1-BP vapors (Sclar 1999; Ichihara et al. 2002; 2004a; 2004b; NTP 2004; Hanley et al. 2006; Majersik et al. 2007; Raymond and Ford 2007). The absence of dermal penetration data prevents the full characterization of the risks associated with occupational exposures to 1-BP and prevents the development of risk management plans capable of adequately protecting workers.

The purpose of this study was to determine the in vitro human epidermal absorption characteristics of 1-BP. Because of its high vapor pressure, the evaporation rate of 1-BP in a fume hood was measured. Different dermal exposure scenarios (infinite dose, finite dose, and transient exposure) using neat 1-BP as donor were studied. Infinite dose exposure to a commercial dry cleaning solvent (DrySolv) consisting of >95% 1-BP by weight was also studied. For comparisons, exposures using saturated aqueous solutions of 1-BP and DrySolv were examined. Finally, the corrosive potential of 1-BP was determined using a cultured reconstructed human epidermal model. Results of this study will be evaluated for the possible assignment of a NIOSH skin notation to 1-BP (NIOSH 2009).

METHODS

1-BP Evaporation Flux Measurement

The rate of evaporation of 1-BP was measured gravimetrically at room temperature (23°C). The experiment was designed as a surrogate to an in vivo dermal toxicity study undertaken by Elf Atochem (1998). In this study 2000 mg/kg body weight of 1-BP was applied to shaved skin of rats, and the application area was wrapped with a gauze pad for 24 h.

Evaporation flux measurements ($n = 4$) were performed in an open fume hood. A Mettler-Toledo balance (PG503-S, Columbus, OH) was used to measure and record 1-BP mass. The balance was open on all sides so as not to impede air flow. An average air speed of 0.3 m/s was measured at the location of the balance's measuring pan using a rotating vane anemometer (TSI VelociCalc Plus, Shoreview, MN). To mimic conditions of the in vivo dermal toxicity study, 0.4 ml of 1-BP (2000 mg/kg × 1 ml/1,350 mg × 0.25 kg average rat weight) was added to a 20-cm^2 glass petri dish and then covered with a 12-ply gauze pad. The mass was recorded at 1-s intervals for 4 min.

In Vitro Dermal Penetration Studies

Standard static in vitro diffusion cell methods were employed using heat-separated epidermal membranes. Studies were performed in an open fume hood similar to the one used for evaporation flux measurements.

Buffer Diffusion cell receptor solution was HEPES-buffered Hanks balanced salt solution (HBSS, Invitrogen, Carlsbad CA) composed of 5.96 g HEPES, 0.32 g $NaHCO_3$, and 0.05 g gentamicin sulfate added to 1000 ml HBSS. The solution was brought to pH 7.4 by titration with NaOH and was degassed by heating to 40°C and stirring under laboratory vacuum for approximately 15 min.

Skin Caucasian female breast or abdominal skin samples from elective surgical procedures were obtained from the West Virginia University Skin Bank. This skin bank maintains Human Subjects Review Board approval and requires informed consent for all collections, but the review board deemed that the specific use of this tissue by us was "not human research" and hence not subject to additional review. Skin was submersed in 60°C buffer for 45 s, and epidermis was teased from dermis using cotton swabs. Epidermal membranes were stored frozen (–85°C on gauze pads saturated with HBSS plus 10% glycerol) prior to use. The use of heat-separated human epidermal membranes accords with guidelines published by the Organization for Economic Cooperation and Development for the conduct of in vitro dermal penetration studies (OECD 2004).

Diffusion Cells Static "Franz-type" diffusion cells (PermeGear, Inc., Hellertown, PA) were used for these studies. Exposed skin surface was 0.64 cm^2 and receptor volumes were 5 ml. A heater/recirculator was used to maintain the receptor compartments at 37°C. Skin surface temperatures ranged from 32 to 33°C. Skin discs were mounted on diffusion cells and allowed to equilibrate overnight prior to 1-BP exposures.

Dosing Solutions and Exposures The following dosing regimens were performed: (1) neat 1-BP, infinite dose; (2) saturated aqueous 1-BP, infinite dose; (3) neat 1-BP, finite dose; (4) neat 1-BP, transient exposure to infinite dose. 1-BP (purity 99%) was obtained from Sigma-Aldrich (Saint Louis, MO). In addition, a commercial dry cleaning formulation, DrySolv (Enviro Tech International, Inc., Melrose Park, IL), containing, according to the material safety data sheet (MSDS), >95% 1-BP with additives for stabilization, was applied as (5) neat, infinite dose, and (6) saturated aqueous solution, infinite dose. For saturated solutions, excess solvent was vigorously mixed with water at 32°C on a reciprocating shaker (FinePCR Microshaker, Daigger Lab Equipment, Vernon Hills, IL) for approximately 24 h. The finite dose was 10 $\mu l/cm^2$ skin surface, equivalent to 13.5 mg/cm^2. For transient exposure, 1-BP was applied to donor compartments and removed after 10 min of exposure. Skin surfaces were wiped with cotton swabs to remove excess 1-BP. For each exposure, nine membranes were studied, with three membranes from each of three individual donors. For infinite dose and transient exposures, donor cell tops were capped and receptor arm ports were covered with parafilm to inhibit evaporative losses. For the finite dose exposures, donor cell tops were left open to the atmosphere to simulate splash-type of exposures.

Receptor Cell Sampling Samples (250 μl) were placed in 10-ml screw-top headspace vials with Teflon septa and stored on a cooled (4°C) tray prior to analysis within 8 h of sampling. Receptor samples were

replaced with fresh buffer. Use of crimp-top vials with no cooling resulted in gradual sample losses up to 25% over 24 h of storage. The use of screw-top caps and sample cooling reduced losses to 3–7% over the same period. No modifications to the analysis were made to compensate for these losses.

1-Bromopropane Quantification

1-BP concentrations in receptor samples were quantified by gas chromatography with flame ionization detection (Varian 3800, Walnut Creek, CA), using a trifluoropropylmethyl polysiloxane capillary column (Restek Rtx 200 MS, 30 m length, 0.25 mm ID, 1 μm thickness; Bellefonte, PA) with 1 ml/min of He gas flow. Automated sample analysis was performed using a CombiPal autosampler (CTC Analytics, Zwingen, Switzerland). Samples were heated to 60°C for 10 min. A 500-μl headspace sample was injected into the GC (injector temperature 150°C, split ratio 4) using a 1-ml gas-tight headspace syringe (Hamilton Bonaduz Ag, Bonaduz, Switzerland) heated to 65°C. The initial oven temperature of 60°C was held for 4.5 min, then ramped to 230°C at 50 °C/min. Retention time for 1-BP was 4.2 min.

Calibration curves (1-BP in HBSS) were generated on the day of each experiment and were linear ($r^2 > 0.995$) over the range of concentrations tested (approximately 0.2–14 μg/ml for finite dose; 14–450 μg/ml for infinite dose exposures).

Water solubility of neat 1-BP and of 1-BP from DrySolv was determined by centrifugation of excess saturated aqueous donor solutions at 32°C, followed by dilution (1:10) with HBSS.

Data Analysis

Mass accumulations of 1-BP in receptor compartments over time were calculated from the measured concentrations. The mass of 1-BP removed through sampling was accounted for. Steady- or pseudo-steady-state fluxes were calculated from infinite dose exposures by dividing the change in mass accumulation by the change in exposure time. Permeability coefficients were calculated by nonlinear regression of the infinite dose mass accumulation curves with a solution to the diffusion equation for a homogeneous membrane, as described previously (Frasch and Barbero 2005). Each exposure represents results of three individual skin samples averaged from three different skin sources (nine skin samples from $n = 3$ sources). Data from all skin samples studied were included in the analyses.

EpiDerm Skin Corrosivity Test

The corrosivity of 1-BP was determined using the EpiDerm human reconstructed epidermis model (MatTek Corp., Ashland, MA). For comparison, tetrachloroethylene was also included in the same test. The standard protocol developed by the company was followed (http://www.mattek.com/pages/pdf/INVITTOX-119 - EpiDerm - Skin-Corrosivity-Protocol.pdf). Briefly, tissues were pre-incubated (37°C, 5% CO_2) in culture medium for 1 h prior to dosing. Four EpiDerm tissues were then exposed to 1-BP and four to tetrachloroethylene. Sufficient solvent was applied to ensure its presence over the durations of exposure. In addition, negative (H_2O) and positive (8 *N* KOH) controls were performed, with 50 μl added to each of 4 tissues. Exposures were 3 min (2 tissues per treatment) and 1 h (2 tissues per treatment). After thorough rinsing with phosphate-buffered saline (PBS), tissues were transferred to MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay buffer and incubated for 3 h (37°C, 5% CO_2). After rinsing with PBS and drying, tissues were immersed overnight in isopropanol at room temperature to extract formazan dye. The optical density of the extracted formazan was determined spectrophotometrically at 570 nm, and cell viability was calculated as a percentage of the mean of the negative (water exposed) control tissues. In accordance with the recommendations of the manufacturer, the test substance is classified as "corrosive" to skin if the viability after a 3-min exposure is <50%, or if the viability after a 1-h exposure is <15%.

RESULTS

1-BP Evaporation Flux

Half of the mean initial measured mass of 1-BP (520 mg, $n = 4$) evaporated in 100 s. Thus, evaporation flux (J_{evap}) was:

$$J_{evap} = \frac{260\,\text{mg}}{20\,\text{cm}^2\,(100/3600)\,\text{h}} = 470\,\text{mg}\cdot\text{cm}^{-2}\cdot\text{h}^{-1}. \quad (1)$$

At the skin surface temperature of 32°C, this flux would be even higher (see Appendix). This measured flux can be compared with the quantity calculated using a method employed by the U.S. Environmental Protection Agency (EPA) to estimate evaporation from chemical spills (see Appendix).

In Vitro Dermal Penetration Studies

Results of all penetration studies are summarized in Table 2.

1-BP Solubility The measured solubility of 1-BP in water at 32°C (Table 1) was 2276 ± 30 μg/ml (mean ± SD, $n = 3$). Aqueous solubility of 1-BP from DrySolv was 2450 ± 166 μg/ml ($n = 4$). These measurements are similar to other published 1-BP solubilities (Yalkowsky and He 2003).

Infinite Dose, Neat 1-BP Results are displayed in Figure 1. The total 1-BP that penetrated skin over 3 h of exposure was 1876 ± 527 μg/cm^2 (mean ± SD, $n = 3$). This leads to an average flux of 625 ± 176 μg cm^{-2} h^{-1}. The initial flux, measured over the first 30 min of neat 1-BP exposure, is 960 ± 138 μg cm^{-2} h^{-1}.

Diffusion theory holds that infinite dose exposures applied to a homogeneous membrane result in penetration curves that approach linearity after an initial lag time. The concave shape of the 1-BP penetration curve raises the possibility of problems or errors with these experiments. Because the exposure was to neat 1-BP and visual verification of the presence of donor throughout the experiment was confirmed, donor depletion cannot explain the shape. In 1 of 3 experiments, receptor concentration of 1-BP exceeded 10% of saturation at the 2.5- and 3-h timepoints. However, this excess receptor accumulation does not appear adequate to explain the shape of the penetration curve. It may be that 1-BP alters the skin barrier properties. For example, dehydration of the stratum corneum following application of 1-BP might induce a decrease in permeability (Hikema and Maibach 2006; Shah et al. 2008), evidenced by a concavity in the penetration curve as recorded here. Because these data (and data from infinite dose DrySolv exposure, displayed in Figure 5) fail to evince a steady-state penetration rate, permeability coefficients were not calculated for these exposures.

Infinite Dose, Saturated 1-BP Figure 2 displays these results. The total 1-BP that penetrated skin over 3 h of exposure was 1635 ± 857 μg/cm^2 (mean ± SD, $n = 3$). The permeability coefficient was

TABLE 2. Summary of 1-BP Epidermal Penetration Results

Exposure	k_p (cm/h)	J_{ss} (μg cm^{-2} h^{-1})	m (μg/cm^2)
Infinite dose, neat 1-BP		625 ± 176 to 960 ± 138	
Infinite dose, saturated 1-BP	0.257 ± 0.141	585 ± 320	
Finite dose, neat 1-BP			22 ± 14
Transient exposure, neat 1-BP			179 ± 78
Infinite dose, neat DrySolv		441 ± 116 to 722 ± 501	
Infinite dose, saturated DrySolv	0.263 ± 0.092	644 ± 225	

Note. k_p: Permeability coefficient. J_{ss}: steady-state (or pseudo-steady-state) flux. m: Total penetrated mass per area exposed skin. "Saturated" refers to saturated aqueous solution. Blank cells indicate values that cannot be calculated from the data or are irrelevant based upon the exposure. Where a range of J_{ss} is given, lower value indicates time-averaged flux over 3-h exposure; higher number is initial (30-min) flux. All data are mean ± SD. Each exposure represents data from nine individual skin samples, three each from $n = 3$ skin sources.

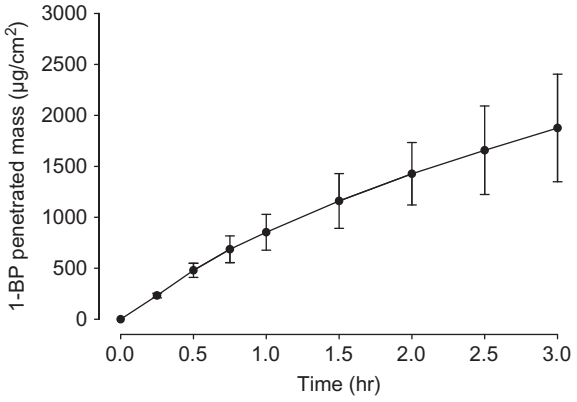

FIGURE 1. Time course of penetration of 1-BP from infinite dose of neat donor. Mean and standard deviation from 3 different skin sources.

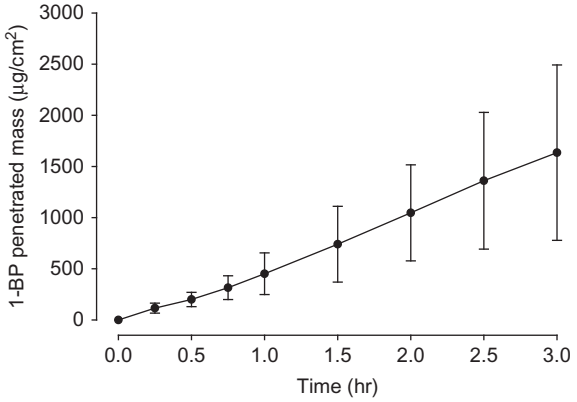

FIGURE 2. Time course of penetration of 1-BP from infinite dose saturated aqueous donor. Mean and standard deviation from three different skin sources.

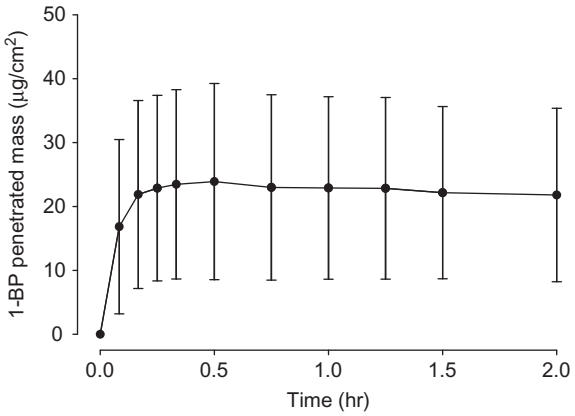

FIGURE 3. Time course of penetration of 1-BP from finite dose of neat donor. Dose was 10 µl/cm² (= 13.5 mg/cm²). Mean and standard deviation from three different skin sources.

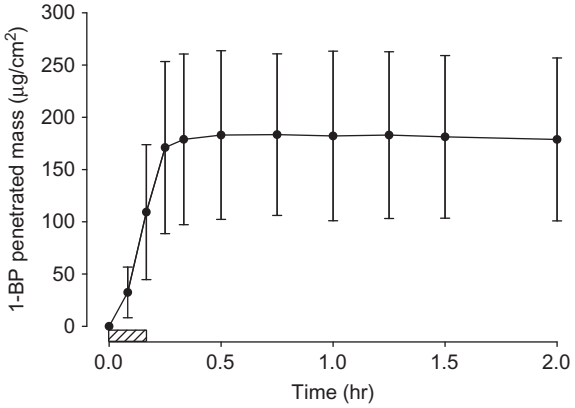

FIGURE 4. Time course of penetration of 1-BP from transient exposure to neat donor. Exposure duration was 10 min (hatched area on time axis). Mean and standard deviation from three different skin sources.

0.257 ± 0.141 cm/h, and average steady-state flux was 585 ± 320 µg cm^{-2} h^{-1}.

Finite Dose, Neat 1-BP These results are displayed in Figure 3. The total 1-BP that penetrated the nonoccluded skin was 22 ± 14 µg/cm² (mean ± SD, $n = 3$). This corresponds to an average penetration of 0.16% of the applied dose of 13.5 mg/cm². The large standard deviation in this measurement is indicative of the difficulty in spreading the small, rapidly evaporating dose evenly over the exposed skin surface.

Transient Exposure, Neat 1-BP Results are shown in Figure 4. Following a 10-min exposure to an infinite dose, 179 ± 78 µg/cm² (mean ± SD, $n = 3$) 1-BP penetrated the skin and accumulated in receptor compartments. Note that receptor cell accumulation persists well after the exposure time. This amount can be compared with the amount predicted by a simple equation posited in a recent analysis of the transient dermal exposure (Frasch and Barbero 2008):

$$m = J_{ss} t_{exp} \quad (2)$$

where m is penetrated mass per unit area, J_{ss} is the steady-state flux for a volatile compound, and t_{exp} is the exposure time. For a 10-min exposure time and a flux of

960 μg cm^{-2} h^{-1}, Eq. (2) predicts a penetrated mass of 160 μg/cm^2 of exposed skin surface. These transient 1-BP exposure data support the use of Eq. (2) to predict total penetrated mass from measured steady-state fluxes.

Infinite Dose, Neat DrySolv Figure 5 displays these results. The total penetration of after a 3-h infinite dose exposure to DrySolv was 1322 ± 348 μg/cm^2 (mean ± SD, $n = 3$), for an average flux of 441 ± 116 μg cm^{-2} h^{-1}. The concave shape of the penetration curve is similar to that following neat 1-BP exposure (Figure 1), and the initial flux measured over the first 30 min of exposure is 722 ± 501 μg cm^{-2} h^{-1}.

Infinite Dose, Saturated DrySolv Results are displayed in Figure 6. The total 1-BP that penetrated skin over 3 h of exposure was 1831 ± 631 μg/cm^2 (mean ± SD, $n = 3$). The permeability coefficient was 0.263 ± 0.092 cm/h, and average steady-state flux was 644 ± 225 μg cm^{-2} h^{-1}.

EpiDerm Skin Corrosivity Test

1-BP is considered noncorrosive according to the results of this test. A 3-min exposure resulted in average cell viability of 101% of water-exposed control, while a 1-h exposure resulted in 22% viability, above the threshold of 15% required for a designation of corrosive. The corresponding cell viability percentages for tetrachloroethylene exposures were 120 and 47%, respectively.

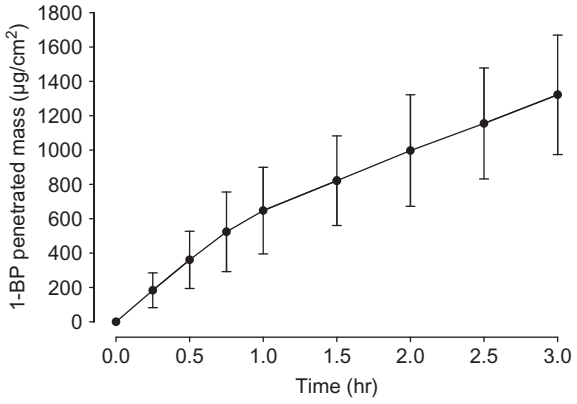

FIGURE 5. Time course of penetration of 1-BP from infinite dose of neat DrySolv donor. Mean and standard deviation from three different skin sources.

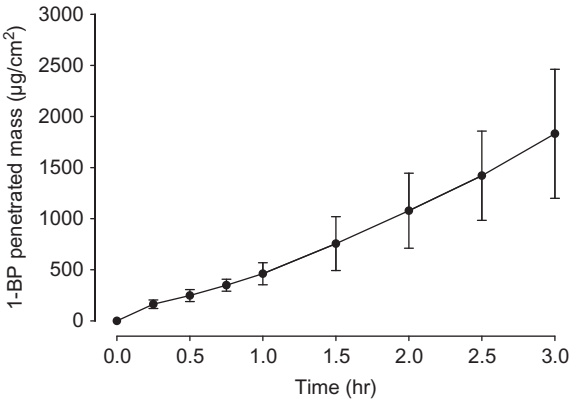

FIGURE 6. Time course of penetration of 1-BP from infinite dose of saturated aqueous DrySolv donor. Mean and standard deviation from three different skin sources.

DISCUSSION

It is important to characterize the dermal penetration characteristics and corrosive potential of 1-BP so that an appropriate hazard-specific dermal risk assessment of this increasingly widely used chemical can be made. This type of information is used by NIOSH and other U.S. and international agencies to assess the potential for both local and systemic adverse effects resulting from skin exposures. The assessment of dermal uptake of substances can also be applied to aid in the refinement of risk management plans and occupational exposure limits (OEL) in settings where exposures may occur through multiple pathways. For example, most OEL are intended to protect workers from inhalation exposure. When situations occur where dermal exposures are also documented, it is important to adjust OEL to account for the contribution of systemic doses from dermal uptake. Failure to do so may result in workers experiencing an aggregate exposure that places them at increased adverse health risk.

Owing to its chemical properties (Table 1), this small, moderately lipophilic solvent may be expected to readily penetrate skin upon dermal exposure. However, apparently no data existed

prior to this study to corroborate this suspicion. There is one reported dermal toxicity study in rats reported by the Elf Atochem Company, in which 2000 mg/kg body weight of 1-BP was applied to shaved skin and wrapped with a gauze pad for 24 h. After 2 wk, there were no signs of dermal toxicity, and the study concluded that the dermal LD_{50} exceeds 2000 mg/kg (Elf Atochem 1998). Results of this study led the American Conference of Governmental Industrial Hygienists to conclude that "there is no basis for a skin notation" (ACGIH 2005) for 1-BP. However, the dermal exposure in that study is questionable owing to the rapid evaporation of this highly volatile compound. In our surrogate evaporation studies, half of the initial 1-BP evaporated within 100 s and essentially all was gone at 4 min. Such a rapid evaporation rate raises questions as to the appropriateness of the application method in this dermal toxicity study: Very little of the applied dose was available for dermal penetration. It remains unknown whether a dermal applied dose of 2000 mg/kg might lead to toxic endpoints if an occlusive dressing that prevented evaporation were applied. In the workplace, the potential for occlusion under chemical protective clothing needs to be considered.

Results of in vitro dermal absorption studies described here demonstrate the potential for substantial dermal penetration of 1-BP, dependent upon the type and duration of exposure. Neat 1-BP, when applied as an infinite dose (Figure 1), penetrated skin at a rate of between 625 and 960 $\mu g\ cm^{-2}\ h^{-1}$. Magnusson et al. (2004) recommended that permeants with fluxes exceeding 3.02×10^{-6} mol $cm^{-2}\ h^{-1}$ be classified as "good" penetrants. Our measured time-averaged flux of 625 $\mu g\ cm^{-2}\ h^{-1}$ corresponds to 5.08×10^{-6} mol $cm^{-2}\ h^{-1}$, and therefore 1-BP would be classifiable as a "good" penetrant, even if the 3-h time-averaged flux represents an underestimation of the initial, more linear rate of penetration. While these infinite dose exposures are not representative of typical occupational or environmental exposures, such data are essential in deriving steady-state flux values and permeability coefficients. These in turn are used in the dermal risk assessment process to establish estimates of the dermal absorption potential of a chemical.

Fluxes of this magnitude through human skin are not unusual for organic solvents. For example, a recent review of dermal absorption studies of benzene (Williams et al. 2011) reported steady-state dermal fluxes of neat benzene and benzene-saturated aqueous donor to range from 200 to 400 $\mu g\ cm^{-2}\ h^{-1}$. Benzene has comparable physical properties to 1-BP: MW (78), log K_{ow} (2.13), vapor pressure (95 mm Hg at 25°C), and water solubility (1800 μg/ml). Ethanol flux was found to range from 900 to 4200 $\mu g\ cm^{-2}\ h^{-1}$ (Berner et. al. 1989).

While infinite dose exposures demonstrate substantial fluxes of 1-BP, the finite dose penetration data (Figure 3) demonstrate that only a small percentage (0.16%) of the applied dose penetrated the skin. According to the NIOSH strategy for assigning skin notations (NIOSH 2009), a 10% absorption rate was selected as the critical cutoff value to differentiate between low and high dermal absorption. Therefore, according to this criterion, 1-BP would not be considered to be dermally absorbed to a significant extent from a finite dose under the present experimental conditions. This finite dose experiment is a model for splash-type occupational exposures. 1-BP has a high vapor pressure (Table 1) and rapidly evaporates from the unoccluded skin surface. Our measured evaporation flux is approximately 500× greater than our measured steady-state dermal flux. The high rate of evaporation of this compound compared with the dermal penetration rate would explain these results.

The potential for dermal corrosion, defined as an irreversible tissue damage following skin contact, is an important consideration in establishing procedures for the safe handling of chemicals. The updated NIOSH skin notation process (NIOSH 2009) recognizes the hazards associated with dermal corrosion with a [SK:DIR(COR)] notation. EpiDerm and other corrosivity tests using human skin models have been validated by both the European Center for the Validation of

Alternative Methods (ECVAM 2000) and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM 2002).

The EpiDerm Dermal Corrosion Measurement System predicts the skin corrosivity potential of a chemical using a cultured three-dimensional human epidermis model. The test is based on the fact that corrosive chemicals are cytotoxic after a short-term exposure. A corrosive chemical penetrates the stratum corneum and is cytotoxic to underlying epidermal tissue. Results from the EpiDerm skin corrosivity test reveal that although there are cytotoxic effects resulting from dermal application of 1-BP, the compound cannot be considered as corrosive based upon established criteria. A 1-h exposure resulted in epidermal cell viability of 22% of water-treated control, above the cutoff value of 15%.

To summarize these findings, the dermal absorption of 1-BP depends strongly on the exposure scenario. Owing to its rapid evaporation rate, only a small amount (<0.2%) of a thin film finite dose application penetrates the epidermis. On the other hand, a substantial uptake rate of 1-BP through epidermis results from infinite dose exposures. Overall 1-BP fluxes from saturated aqueous solutions of 1-BP and DrySolv are similar to fluxes from neat donor applications. 1-BP may induce changes in the barrier property of the skin, but it is noncorrosive when applied to a reconstructed human epidermis model. Results of these studies need to be considered in a dermal risk assessment of this chemical.

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APPENDIX: ESTIMATION OF EVAPORATION FLUX

The U.S. Environmental Protection Agency (U.S. EPA 1999) suggests the use of the following to estimate evaporation from the surface of a pool of liquid, at or near the ambient temperature, for risk management of chemical spills:

$$J_{evap} = \frac{760.8 \cdot P_{vap} \cdot MW^{0.667} \cdot u^{0.78}}{T + 273}, \quad \text{(A1)}$$

where J_{evap} is evaporation flux (mg cm^{-2} h^{-1}), P_{vap} is the vapor pressure of the chemical at the ambient temperature (kPa), MW is (dimensionless) molecular weight, u is wind speed above the liquid surface (m/s), and T is liquid temperature (°C).

Vapor pressure depends on temperature. If it is known at one temperature (T_1), it can be estimated at a different temperature (T_2) using a form of the Clausius–Clapeyron equation (Smith 2004):

$$\ln\left(\frac{P_{vap,2}}{P_{vap,1}}\right) = \frac{\Delta H_{vap}}{R}\left(\frac{1}{T_1 + 273} - \frac{1}{T_2 + 273}\right), \quad \text{(A2)}$$

where ΔH_{vap} is the molar enthalpy of vaporization (J/mol) and R is the gas constant (8.314 J mol^{-1} K^{-1}). For convenience, temperatures T_1 and T_2 are in °C. A value of 32,130 J/mol for ΔH_{vap} of 1-BP (Abboud and Notario 1999) is used here. Thus, the known P_{vap} of 111 mm Hg at 20°C (Table 1) gives a value of 127 mm Hg at the experimental temperature of 23°C. Using this value in Eq. (A1) with a wind speed of 0.3 m/s gives

$$J_{evap} = 420 \text{ mg} \cdot \text{cm}^{-2} \cdot \text{h}^{-1}. \quad \text{(A3)}$$

This result compares favorably with our measured J_{evap} of 470 mg cm^{-2} h^{-1}. This finding supports the use of the U.S. EPA method to estimate evaporation flux in the absence of measurements.

For comparison, at the skin surface temperature of 32°C, Eqs. (A2) and (A1) yield:

$$J_{evap} = 600 \text{ mg} \cdot \text{cm}^{-2} \cdot \text{h}^{-1}. \quad \text{(A4)}$$

Thus, evaporation flux of 1-BP following dermal exposures is likely to be greater than the flux measured herein at room temperature.