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Dermal Disposition of Triazine in Cutting Fluid Mixtures

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ABSTRACT

Triazine is often added as a biocide/preservative to cutting fluids formulations that are used in the metal machine industry. Workers involved in metal machining are not only exposed to components in these cutting fluids, but also to biocides such as triazine that have been implicated in occupational irritant dermatitis. Very little is known about how these cutting fluids and their ingredients influence the dermal disposition of triazine. The purpose of this study was to assess ^{14}C-triazine membrane transport when topically applied to inert silastic membranes and porcine skin in an in vitro flow-through diffusion cell system as aqueous mineral oil (MO) or aqueous polyethylene glycol (PEG) mixtures. ^{14}C-triazine mixtures were formulated with three commonly used cutting fluid additives; namely, 0% or 5% linear alkylbenzene sulfonate (LAS), 0% or 5% triethanolamine (TEA), and 0% or 5% sulfurized ricinoleic acid (SRA). Triazine partitioning from the formulation into the stratum corneum (SC) was reduced significantly by the presence of LAS, while SRA significantly reduced the pH of the formulation. Triazine absorption ranged from 2.2% to 3.9% dose in porcine skin and 12.6% to 18.6% dose in silastic membranes. In silastic membranes, the complete mixture reduced triazine absorption significantly in MO-based mixtures, while in PEG-based mixtures triazine absorption and apparent permeability were significantly increased. In porcine skin, triazine permeability was significantly increased for both MO- and PEG-based complete mixtures with a trend towards greater triazine absorption in more complex PEG-based mixtures. Interestingly, SRA + TEA significantly

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increased triazine permeability absorption in MO- and PEG-based mixtures, but this interaction appears to be more additive than synergistic. Although the physicochemical experiments suggest otherwise, triazine readily permeates a homogenous lipid membrane such as the SC, while triazine permeability was significantly enhanced by the complete mixture, especially in PEG-based mixtures.

Key Words: Triazine; Mixtures; Dermal.

INTRODUCTION

Triazines are often added to a variety of industrial chemicals such as cutting fluids, latex paints, and industrial adhesives to primarily act as a biocide/preservative to prevent slime-forming bacteria and fungi from deteriorating these complex industrial formulations (1). The more common triazine biocides include hexahydro-1,3,5-triethyl-s-triazine (e.g., Vancide TH) (Figure 1), which is the focus of this research, and hexahydro-1,3,5 tris (2-hydroxyethyl)-s-triazine (e.g., Grotan BK) (2). These biocides are known irritants, and have been associated with numerous incidences of occupational contact dermatitis as well as significant macroscopic and cellular response in skin (3–5). Vancide TH is a known dermal irritant, but there is little or no evidence that it is a sensitizer (1). Its chemical homologue, Grotan BK, has often been associated with allergic dermatitis (6,7). It should be noted that ''in use'' concentrations of 1–2% triazine can cause local dermal and eye-irritating effects; however, workers can be exposed to higher concentrations during biocide mixing, and percutaneous absorption may result in significant hepatoxicity (8).

The chemistry of these triazines is an indicator of its potential cutaneous toxicity for individuals handling these biocides. It is very soluble in water, but less soluble in organic solvents (1). Triazine is very alkaline in water (pH of 11 with 5% in water). Irrespective of whether occupational dermatitis is due to irritation or sensitization, triazine must be able to penetrate the skin surface to cause dermatitis, and it's logical to hypothesize that in occupational scenarios where the skin is consistently hydrated, these water-soluble molecules would readily diffuse across the epidermal barrier. This event can become more of a health concern when one recognizes that cutting fluids contain other potential irritants that could also modulate dermal disposition of triazine.

Surprisingly, very little is known about triazine dermal disposition in skin as a single chemical exposure or when there is simultaneous dermal exposure to a variety of formulation additives that usually constitute most commercial cutting fluid formulations.

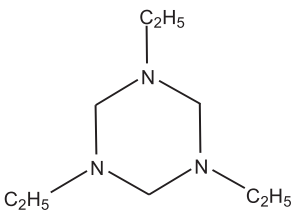

Figure 1. Chemical structure of triazine (1,3,5-triethylhexahydro-1,3,5-triazine).

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Many of the water-based metalworking fluids can be broadly classified as soluble oils. The major components are a mineral oil base, with addition of emulsifiers, and other additives such as anticorrosive agents (e.g., triethanolamine), extreme pressure agents (e.g., polysulfides), and biocides (9,10). The other category of cutting fluids are the synthetic cutting fluids that consist primarily of similar additives, but the mineral oil component is replaced with a synthetic additive such as polyethylene glycol. The focus of this study was to formulate these two categories of cutting fluids with 1) a surfactant/emulsifier (sodium linear alkylbenzene sulfonate, LAS), 2) an anticorrosive agent (triethanolamine, TEA), and 3) extreme pressure agents or lubricants (sulfated fatty acid ester, SRA). Many of these formulations were based in either a soluble oil mixture (e.g., mineral oil + water) or synthetic aqueous fluid mixture (e.g., polyethylene glycol, PEG + water).

The primary objective of this study therefore was to utilize a factorial experimental design and empirically determine the physicochemical properties of these mixtures prior to assessing membrane transport. The aim was to characterize the contribution of each additive to the physicochemical properties of a given cutting fluid mixture. Changes in mixture pH, viscosity, and partitioning behavior of triazine into the stratum corneum were measured to provide a mechanistic insight into chemical interactions influencing triazine transport in skin. The second objective was to assess membrane transport in silastic and porcine skin membranes in a flow-through diffusion cell system.

Silastic membranes are inert materials and are not responsive to the formulation effects as are biological membranes, and therefore any changes in solute transport will strictly reflect unique physicochemical interactions in each mixture. Although these artificial membranes are biochemically distinct from skin and stratum corneum (SC), their very lipophilic properties compared to the more heterogeneous SC encourages partitioning of nonpolar solutes from an aqueous mixture. Porcine skin is anatomically and biochemically similar to human skin (11), and therefore this model system should closely reflect percutaneous absorption into the blood stream without the interference of systemic clearance mechanisms. Assessing diffusion in these two model membrane systems allows one to probe for chemical and biological interactions during an 8-hr occupational exposure, and identify which additive or combination of additives influences the dermal disposition of triazine in a typical occupational exposure scenario.

MATERIALS AND METHODS

Chemicals

Radiolabeled ^{14}C-triazine (hexahydro-1,3,5-triethyl-s-triazine-ring-UL-^{14}C; specific activity = 10.00 mCi/mmol) was obtained from American Radiolabeled Chemicals Inc. (St. Louis, MO). Radiochemical purity was 99.12%. Linear alkylbenzene sulfonate (LAS) was obtained from Aldrich Chemical Company, Milwaukee, WI. Sulfated ricinoleic acid (SRA), triethanolamine (TEA), and mineral oil (MO), were obtained from Sigma Chemical Company, St. Louis, MO, and poly(ethylene glycol), average M.W. 200 (PEG), was obtained from Acros Organics, Morris Plains, NJ. ^{14}C-triazine was dissolved in 50/50 (v/v) water: ethanol, and was used to prepare the surrogate cutting fluid mixtures summarized in Table 1.

Table 1. Triazine (TRI) mixtures prepared in water and either 5% mineral oil or 5% PEG for physiochemical and diffusion studies.

1-Component mixture	2-Component mixture	3-Component mixture	4-Component mixture
TRI	TRI + SRA	TRI + SRA + LAS	TRI + SRA + LAS + TEA
	TRI + LAS	TRI + SRA + TEA	
	TRI + TEA	TRI + LAS + TEA	

Note: PEG = polyethylene glycol 200; SRA = 5% sulfated ricinoleic acid, TRI = 2% triazine; TEA = 5% triethanolamine; LAS = 5% linear alkylbenzene sulfate.

Physicochemical Studies

Viscosity and pH Determinations

Triazine solutions were formulated as described in Table 1 and then tested in a Stresstech Rheometer (Reologica Instruments AB, Lund, Sweden/ATS Rheosystems, Bordentown, NJ) for 5 minutes at 25° C. Using an Excel spread sheet, the time points and viscosity (Pa s) were plotted on a graph to determine the plateau, which is the viscosity. The pH was tested using a Fisher Scientific Accumet AR10 pH meter. Room temperature ranged from 25–28° C, and the meter was calibrated to two points.

Stratum Corneum (SC)/Vehicle Partition Coefficient Determination

SC/Vehicle partition coefficients were determined according to methods previously described in our laboratory (12). In brief, stratum corneum and epidermis layers were removed from abdominal skin of a female weanling Yorkshire pig by heat treatment and then treated with 0.25% trypsin (Sigma Chemical Co., St. Louis, MO) to dissolve the epidermis. The remaining SC was dried and weighed (5–8 mg sample) and placed in vials. About 3 mL of the triazine mixtures (Table 1) with ^{14}C-triazine was added to the SC sample vial (n = 4), capped, sealed, and allowed to remain undisturbed at room temperature for 24 hr. At 24 hr, 10 μL of the vehicle was removed for direct counts using Ecolume (ICN Costa Mesa, CA). The SC sample was removed, gently blotted to remove excess solution, and then analyzed as described below.

Flow-Through Diffusion Cell Experiments

The flow-through diffusion cell system as previously described in the literature (13) was used to perfuse porcine skin and silastic (polydimethylsiloxane) membranes. Porcine skin was obtained from the dorsal area of weanling female Yorkshire pigs. The skin was dermatomed to a thickness of 500 μm with a Padgett Dermatome (Padgett Instruments Inc., Kansas City, MO). Silastic membranes (250 μm) were obtained from Dow Corning Corporation, Midland, MI. Each circular skin and silastic section was punched to provide a dosing surface area of 0.64 cm^2 and then placed into a two-compartment, Teflon, flow-through diffusion cell. Skin and silastic discs were perfused

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using Krebs-Ringer bicarbonate buffer spiked with dextrose and bovine serum albumin and dosed with 20 μL of 2% triazine (625 μg/cm^2) mixtures described in Table 1. The temperature of the perfusate and flow-through cell was maintained at 37° C using a Brinkmann constant-temperature circulator (Brinkmann Inc., Westbury, NY), and the pH was maintained between 7.3 and 7.5. Perfusate flow rate was 4.0 mL/hr, and perfusate samples were collected at 0, 10, 20, 30, 45, 60, 75, 90, 105, 120, 150, 180, 240, 300, 360, 420, and 480 min post dosing. At the end of the perfusion, the dose area was swabbed twice with soapy solution (1% Ivory soap) to determine surface content (Swab 1–2), taped-stripped six times (Tape 1–6) with cellophane tape to determine stratum corneum content, and removed from the skin disc with a 0.64 cm^2 punch biopsy to determine dose area skin deposition. These tissue samples were saved for radiochemical analysis described below.

Chemical Analysis

For determination of ^{14}C-triazine, perfusate, swabs, dose skin, and stratum corneum samples were combusted in a Packard Model 306 Tissue Oxidizer (Packard Chemical Co., Downers Grove, IL) and then analyzed by Packard Model 1900TR Liquid Scintillation Counter (Packard Chemical Co., Downers Grove, IL) for total ^{14}C determination. Triazine stability in the dosing mixtures was confirmed by HPLC-PDA analysis.

Calculations and Statistics

Absorption (% dose) in both model systems was defined as the total percentage of initial dose detected in the perfusate for the entire 8-hr perfusion period. The *apparent permeability* (cm/hr) of triazine in the diffusion cell system was determined from the following equation:

$$\text{Permeability(cm/hr)} = \text{Flux}(\mu\text{g/cm}^2\text{/hr})/\text{Dose}(\mu\text{g/cm}^3)$$

Triazine flux was determined from the apparent steady-state slope derived from a plot of cumulative triazine vs. time. *Tissue disposition* parameters such as surface, stratum corneum (SC), and dosed skin were described above. For *partition coefficient* (PC) determinations, radioactivity content in the vehicle mixture and stratum corneum (SC) were normalized to 1000 mg vehicle ($C_{vehicle}$) and 1000 mg SC (C_{sc}), respectively. $C_{vehicle}$ and C_{sc} represent solute concentrations in the vehicle and SC, respectively. The log SC/Vehicle partition coefficient (Log PC) was determined from the equation:

$$\text{Log PC} = \text{Log}\{C_{SC}/C_{Vehicle}\}$$

Standard errors were determined for all data sets. For analysis of total absorption, permeability, surface, SC, and dosed area data, multiple comparison tests were performed using analysis of variance (ANOVA) with significance level at 0.05. All analyses were carried out using SAS 6.12 for Windows software (SAS Institute Inc., Cary, NC). A least significant difference (LSD) procedure was used for multiple comparisons on all parameters assessed.

RESULTS

Physicochemical Properties of Cutting Fluids

The pH of triazine control mixtures (triazine + water + diluent) was within range of the literature values of pH = 11 (Figure 2). However, SRA or the presence of SRA + LAS, SRA + TEA, or SRA + LAS + TEA decreased mixture pH by at least one pH unit, with SRA alone having the greatest effect on mixture pH. The LAS + TEA mixture appeared to have the greatest effect on mixture viscosity in mineral oil but not synthetic mixtures. The presence of LAS significantly decreased triazine partitioning into the stratum corneum ($p < 0.05$), and this was most significant with complete mixtures and more likely associated with mineral oil than PEG mixtures. The SRA had a similar but not such a significant effect as LAS, while TEA by itself had no effect on triazine partitioning into the stratum corneum.

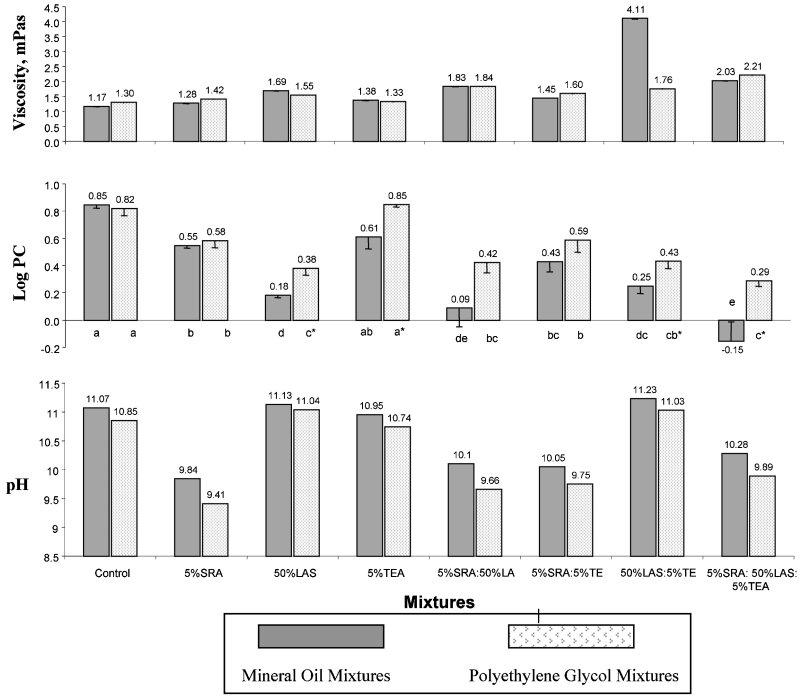

Figure 2. Influence of cutting fluid additives on the physicochemical characteristics of surrogate mineral oil-based and PEG-based cutting fluid formulations. Note: Control refers to triazine only and no other additive present in the mixture. Means with different letters represent significant differences among treatments within a mineral oil- or PEG-based mixture ($p < 0.05$). *Indicates significant differences between mineral oil- and PEG-based mixtures for each treatment.

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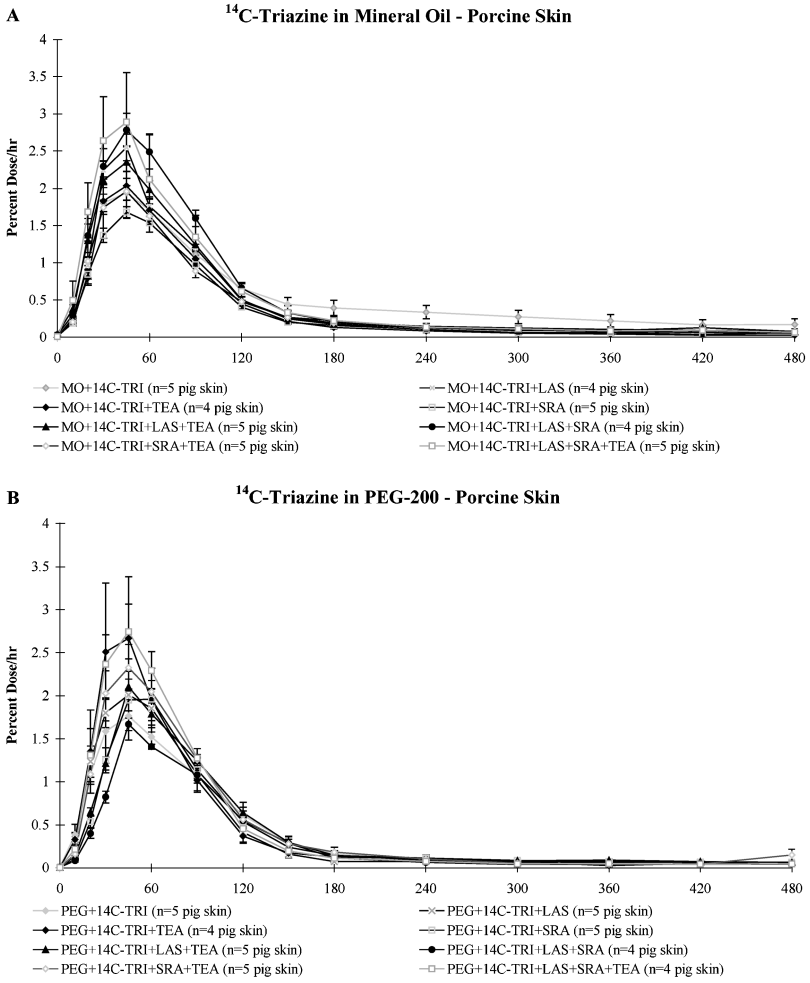

Figure 3. Triazine absorption (% dose) in perfusate from porcine skin exposed topically to mineral oil (A) and PEG (B) cutting fluid mixtures for 8 hr. Note: Control refers to triazine only and no other additive present in the mixture.

Dermal Absorption and Permeability

Triazine absorption peaked rapidly in both silastic membranes (flux profiles not presented) and porcine skin (Figure 3), and rapidly declined to low levels for the remaining 8-hr exposure. Triazine absorption ranged from 12.61–18.63% dose in silastic membranes and 2.41–3.89% dose in porcine skin sections.

In silastic membranes (Figure 4) exposed to PEG mixtures, LAS alone had no effect on triazine absorption, TEA alone decreased absorption, and SRA alone and all other mixtures significantly increased triazine absorption ($p < 0.05$). The SRA + TEA

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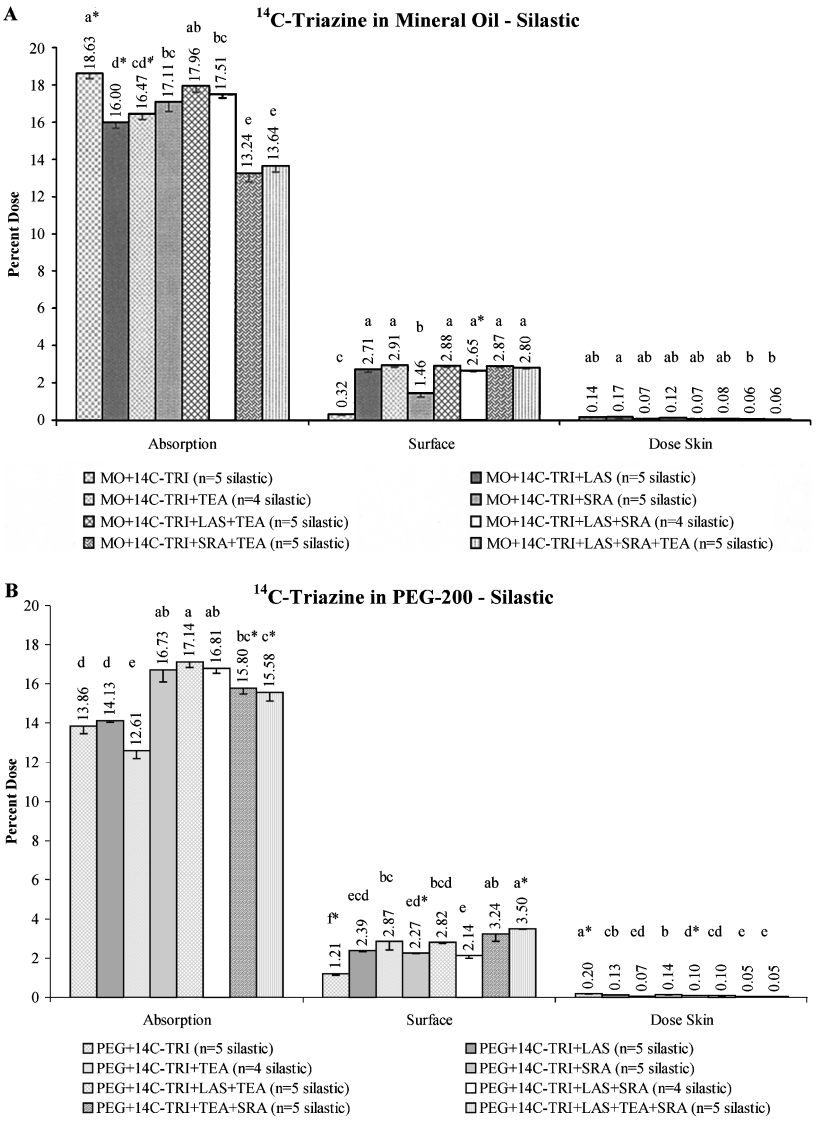

Figure 4. Triazine absorption (% dose) in mineral oil-based (A) and PEG-based (B) mixtures in silastic diffusion cells over 8 hr. Note: Control refers to triazine only and no other additive present in the mixture. Means with the same letters represent no significant differences among treatments within a mineral oil- or PEG-based mixture ($p > 0.05$). *Indicates significant differences between mineral oil- and PEG-based mixtures for each treatment.

and complete mixtures significantly increased triazine permeability. For mineral oil mixtures, there was a reverse trend as additives were formulated into these surrogate mixture; that is, the presence of one or more additives significantly reduced triazine absorption with the complete mixture having the most significant effect. Of interest, only SRA and SRA + TEA appeared to increase triazine permeability, if not significantly, for all

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mixtures involved. The silastic membrane/skin permeability ratio for triazine ranged from 7.09 to 17.01 in mineral oil mixtures and 6.00 to 14.14 in PEG mixtures. The greatest silastic/skin permeability ratios were associated with SRA in mineral oil mixtures (17.01) and with SRA + LAS (14.14) in PEG mixtures.

In porcine skin (Figure 5), a trend similar to triazine absorption in silastic membranes was observed with the PEG mixtures, although the differences were not

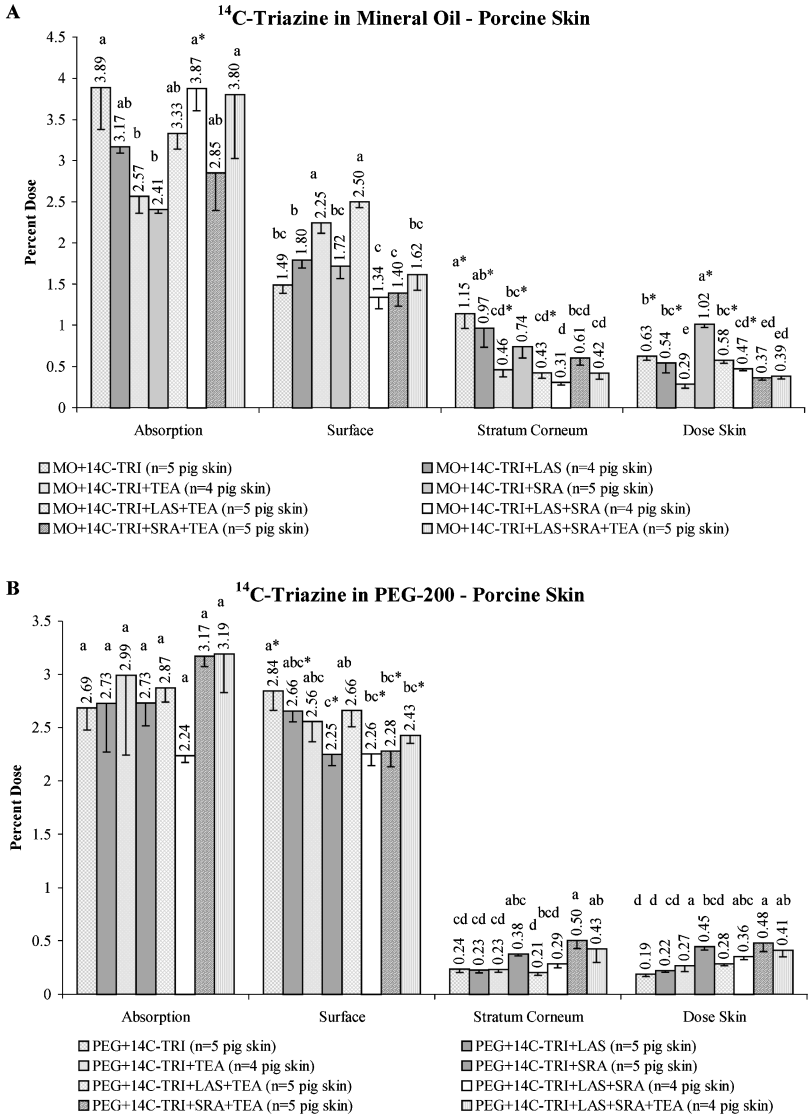

Figure 5. Triazine absorption (% dose) in mineral oil-based (A) and PEG-based (B) mixtures in porcine skin diffusion cells over 8 hr. Note: Control refers to triazine only and no other additive present in the mixture. Means with the same letters represent no significant differences among treatments within a mineral oil- or PEG-based mixture ($p > 0.05$). *Indicates significant differences between mineral oil- and PEG-based mixtures for each treatment.

Table 2. Mean (SEM) apparent permeability of ^{14}C-triazine mixtures.

Mixture	Mineral oil	PEG-200
Silastic membrane	Permeability[†] (cm/hr $\times$ 10^{-3})	Permeability (cm/hr $\times$ 10^{-3})
14C-TRI	(n = 0) N/A	(n = 5) 8.3 (0.51)^{bc}
14C-TRI + LAS	(n = 4) 10.61 (0.19)^{c*}	(n = 5) 7.1 (0.13)^{c}
14C-TRI + TEA	(n = 4) 11.32 (0.39)^{bc*}	(n = 4) 7.2 (0.47)^{c}
14C-TRI + SRA	(n = 1) 14.29 (0.0)^{a}	(n = 4) 10.1 (1.45)^{b}
14C-TRI + LAS + TEA	(n = 5) 12.42 (0.35)^{b*}	(n = 5) 10.1 (0.92)^{b}
14C-TRI + LAS + SRA	(n = 4) 11.86 (0.18)^{bc*}	(n = 4) 9.9 (0.21)^{b}
14C-TRI + SRA + TEA	(n = 5) 14.16 (0.54)^{a}	(n = 5) 14.1 (0.40)^{a}
14C-TRI + LAS + SRA +2 TEA	(n = 5)11.92 (0.62)^{bc}	(n = 5) 15.0 (0.33)^{a*}
Pig skin		
14C-TRI	(n = 5) 0.78 (0.04)^{b}	(n = 5) 0.7 (0.12)^{d}
14C-TRI + LAS	(n = 4) 1.00 (0.06)^{b}	(n = 5) 0.8 (0.10)^{cd}
14C-TRI + TEA	(n = 4) 0.83 (0.08)^{b}	(n = 4) 1.2 (0.32)^{bc}
14C-TRI + SRA	(n = 5) 0.84 (0.03)^{b}	(n = 5) 0.8 (0.05)^{cd}
14C-TRI + LAS + TEA	(n = 5) 0.76 (0.07)^{b}	(n = 5) 0.8 (0.04)^{cd}
14C-TRI + LAS + SRA	(n = 4) 1.02 (0.08)^{b*}	(n = 4) 0.7 (0.01)^{d}
14C-TRI + SRA + TEA	(n = 5) 1.21 (0.25)^{ab}	(n = 5) 1.4 (0.14)^{ab}
14C-TRI + LAS + SRA + TEA	(n = 5) 1.68 (0.37)^{a}	(n = 4) 1.6 (0.18)^{a}

Note: [†]Means with the same letters represent no significant differences between treatments within a mineral oil- or PEG-based mixture ($p > 0.05$).

*Indicates significant differences among mineral oil- and PEG-based mixtures for each treatment. PEG = polyethylene glycol 200; SRA = 5% sulfated ricinoleic acid, TRI = 2% triazine; TEA = 5% triethanolamine; LAS = 5% linear alkylbenzene sulfate.

statistically significant. Interestingly, SRA + TEA and the complete mixture significantly increased the apparent permeability of triazine in PEG mixtures (Table 2). In mineral oil mixtures, the complete mixture also significantly increased triazine permeability, and although SRA or TEA alone significantly reduced triazine absorption, they increased triazine permeability when combined.

Membrane and Skin Deposition

In silastic membranes, triazine deposition in the membrane at 8 hr significantly decreased with the presence of one or more additives in PEG mixtures, and although not statistically significant in mineral oil mixtures, a consistent trend was observed. In the porcine-dosed skin, triazine deposition followed a similar trend with mineral oil mixtures, but deposition was significantly reversed in PEG mixtures. It should be noted that porcine skin retained more of the triazine (0.19–1.02% dose) than did the silastic membranes (0.05–0.2% dose), and that triazine was more likely to be retained in the skin with mineral oil mixtures than PEG after an 8-hr exposure.

Finally, triazine deposition in stratum corneum at 8 hr was significantly reduced by the presence of additives in mineral oil, but the trend was reversed in PEG mixtures.

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This trend in mineral oil mixtures is consistent with the partitioning studies. As with dosed skin, triazine was more likely to be retained in the stratum corneum with mineral oil mixtures than with PEG after an 8-hr exposure, and triazine levels ranged from 0.31–1.15% dose with mineral oil mixtures to 0.21–0.50% dose with PEG mixtures.

DISCUSSION

Workers involved in the manufacturing or use of industrial chemicals are more likely to be exposed to complex chemical mixtures than a single chemical in any given 8-hr workday. These industrial chemicals can be acids, alkalis, detergents, and solvents, including water. A common sequel of these occupational exposures is irritant contact dermatitis that impacts worker health, sick days, and productivity (14). This study prepared surrogate cutting fluid mixtures representing the more commonly used soluble oil and synthetic products used in the metal machining industry to identify those additives or group of additives that will influence dermal absorption and dermal deposition after an 8-hr occupational exposure. Theoretically, each cutting fluid additive can alter the physicochemical nature of these cutting fluid mixtures, and thus the dermal disposition of triazine. This study demonstrated that more than one of these cutting fluid additives modified the physicochemical properties of a simple triazine mixture, and simultaneously altered triazine permeability across skin. This was most evident with complete PEG mixtures in inert and biological membranes.

Triazine is a very water soluble biocide, and therefore does not readily diffuse or partition into skin or a related lipophilic membrane. In spite of this, it was still surprising that many of the cutting fluid additives or combinations of additives, which are also dermal irritants, significantly reduced triazine partitioning into the stratum corneum. It is plausible to assume that these additives increased polarity and solubility of the mixture, making it less favorable for triazine to partition from the mixture into the stratum corneum. As SRA significantly reduced mixture pH by 1–2 pH units, it is safe to assume that this influenced the polarity of triazine, which is a weak base. According to the Henderson-Hasselbalch pH-partitioning hypothesis, this interaction can result in more ionized molecules that are less likely to diffuse across or into a lipophilic membrane such as the SC (15,16). However, this does not support our observations that LAS had no effect on mixture pH, but did consistently and significantly reduce triazine partitioning more so than SRA. A more plausible explanation may be related to the interaction between triazine and LAS micelles, especially as these dosing mixtures contained supra-micellar concentrations at 5% LAS (17). The influence of micelles on membrane diffusion of various drugs and toxicants has been well documented (18).

Prior to this study, triazine absorption had not been reported in the literature, although the Environmental Protection Agency (EPA) had expressed concerns about its corrosive activity in skin (1). The present in vitro study demonstrated that while absorption in silastic membrane can be considerable (12–18% dose), absorption is significantly less in porcine skin (2–4% dose). This difference can be attributed to the more heterogenous composition of skin that contains aqueous domains that are more likely to retain polar triazine molecules than the homogenous lipophilic silastic membrane where triazine will readily partition from the membrane into the aqueous perfusate (13). Also, this study demonstrated that triazine absorption in porcine skin was comparable to literature values for other triazines that are less toxic to skin. Dermal

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absorption of the more lipophilic triazine derivative, atrazine (log $K_{o/w}$ = 2.7), and the explosive, trinitro-1,3,5-triazine, was less than 5% dose within 24 hr in human and pig skin in vitro models (19,20). A more recent study also determined that the permeability of atrazine in mouse skin was 7.69×10^{-4} cm/hr (21), which is within range of what we observed for triazine permeability (7.8×10^{-4} to 16.8×10^{-4} cm/hr) in porcine skin.

Mixture effects on triazine absorption and permeability in porcine skin appeared to be related to cutting fluid additives as well as the diluent effects of mineral oil and PEG. The SC partitioning data, as well as the silastic membrane data, suggest that triazine diffusion should be limited by the presence of several of these additives in either diluent. Surprisingly, triazine permeability was increased significantly with several complex mixtures in either diluent, which is not predictable from the partitioning data. A plausible explanation for this observation may be related to the fact that these additives increased diffusivity by altering polar transport pathways in biological membranes even though partitioning into the SC and silastic membrane was compromised by these additives. Dermal diffusion of hydrophilic solutes such as triazine are more likely to occur via so-called ''polar'' or ''pore'' routes that are conceptually imperfections in the lipid bilayers (22–24). There is convincing evidence that hydration can lead to induction of new pores and reduced tortuosity/path length of existing pores in porcine skin sections, especially for hydrophilic solutes in aqueous environments utilized in this study (25).

It is worth noting that the trend for increased triazine absorption in PEG mixtures was observed in both silastic as well as porcine skin membranes, and supports the fact that PEG was more effective than mineral oil at solubilizing mixture additives and probably behaved as a cosolvent for triazine and other cutting fluid additives (26–28). The SC partitioning data support this argument as PEG was more likely to enhance triazine partitioning into the SC than mineral oil, especially in complete mixtures.

The permeability data also demonstrated that SRA + TEA significantly enhanced triazine diffusion in complex cutting fluid mixtures in either PEG- or mineral oil-based mixtures and in both membrane systems. Sulfated ricinoleic acid is a fatty acid, and although very little is known about its enhancer properties, several investigators have demonstrated that a related fatty acid, oleic acid, is a very effective transdermal enhancer (29,30) with significantly greater enhancement with hydrophilic than hydrophobic drugs (31). One recent study, however, has demonstrated that ricinoleic acid is a less effective permeation enhancer than oleic acid for polar drugs (32). Our study also demonstrated that SRA or SRA + LAS had the greater effect on triazine permeability in silastic membranes than in skin. It is plausible to infer from these membrane comparisons that SRA may have enhanced triazine permeability in silastic membranes by increasing the availability of triazine as well as behaving as a permeation enhancer in the lipophilic silastic membranes. This physicochemical interaction may be characteristic of polar solutes similar to triazine in similar membranes, but may not be applicable to nonpolar solutes as observed with other fatty acids.

Triethanolamine is an alkanolamine, and the enhancer properties of this class of chemicals have also been well documented (33,34). It is no surprise that this pair of additives (TEA + SRA) had the most significant effect on triazine permeability across both membrane systems. Other dermal absorption studies with chemically related compositions have proposed formation of a lipophilic ion pair as a possible mechanism for skin penetration enhancement (35). However, our SC partitioning experiments do not support this hypothesis as SRA or SRA-containing mixtures did not enhance triazine

partitioning into the SC. Finally, the physicochemical and diffusion data demonstrated that LAS did not enhance triazine diffusion in these mixtures, which is not entirely unusual for anionic surfactants (36).

It should also be noted that the addition of additives to mineral oil-based mixtures significantly decreased stratum corneum and skin depostion of triazine, while this was reversed with PEG. The latter reflects the penetrating enhancer effect of PEG over mineral oil in biologically intact membranes (i.e., skin sections) in the presence of several of these additives. The finding that these additives significantly reduced triazine deposition into the silastic membrane, but increased deposition in viable skin, supports the argument that these additives in the presence of PEG promote triazine diffusion via a chemico-biological mechanism as reflected in the permeability data previously described.

Although tissue levels are significantly greater with many of the mineral oil mixtures than with PEG, tissue levels for complete mixtures in both diluents were similar. This has toxicological implications, because if this trend continues with addition of more cutting fluid additives to PEG-based cutting fluids, then these mixtures may be more of an occupational concern than mineral oil where the increasing presence of additives has the opposite effect on tissue deposition. The latter will influence local irritation and the former may enhance absorption, which influences systemic toxicity. This research was focused on interactions with four other cutting fluid additives, but in the real world there is simultaneous dermal exposure to numerous other additives as well as cutting fluid contaminants. In fact, triazine has been implicated with the increased presence of nitrosodiethanolamine in several cutting fluid formulations (37), which may not only be a carcinogenic concern, but may also modulate dermal absorption of triazine.

In conclusion, these physicochemical studies demonstrated that several of the additives did not enhance partitioning into the stratum corneum, but significantly enhanced the apparent permeability of triazine in both membrane systems especially in PEG. The significant enhancer effects in silastic membrane as well as increased deposition in the stratum corneum and skin, especially with PEG mixtures, is suggestive of a significant chemical mechanism associated with these apparent triazine-additive interactions. The subsequent promotion of apparent triazine permeability in skin may be related to these interactions as well as bio-membrane alterations that are often manifested as acute irritant dermatitis in metal machine workers.

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