CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-084

MEDICAL REVIEW(S)

Medical Officer's Review of NDA# 21-084

1. General Information

JAN 19 2000

Applicant identification

Name: Office of the Surgeon General
Department of the Army
Commander, U.S. Army Medical Research and Material Command

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Associated INDs
IND —— Indication: [redacted]

Submission/Review Dates

Date of submission: August 18, 1999

CDER Stamp Date: August 19, 1999

Date Review Completed: January 7, 2000

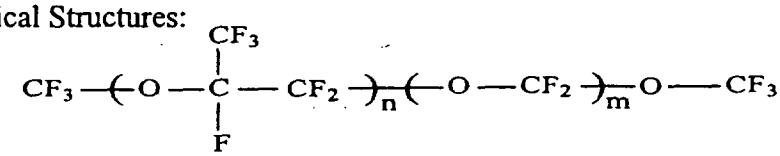
Drug Identification

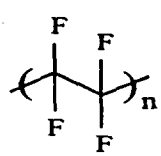
Generic Name: ICD 2289

Proposed Trade Name: Topical Skin Protectant (TSP)

Chemical Name: Polytetrafluoroethylene (PTFE) 50%/
Perfluoroalkylpolyether (PFPE) 50% mixture

Chemical Structures:

PFPE: 

PTFE: 

Molecular Formula: PTFE: $(CF_2CF_2)_n$
PFPE: $(C_xF_{2x+1}\text{-}(O\text{-}CF(CF_3)\text{-}CF_2)_n\text{-}(O\text{-}CF_2)_m\text{-}O\text{-}C_yF_{2y+1}$

(x, y= 1,2, or 3 and n/m>40)

Molecular Weight of PFPE: 3200

Pharmacologic Category: barrier to dermal irritants/allergens

Dosage Form: paste

Route of Administratation: Topical

Proposed Indication & Usage section:
From the proposed label:

[ ]

Proposed Dosage & Administration section:
From the proposed label: ' The application frequency is not specified in the proposed package label.

Related Drugs:
None

Material Reviewed:
NDA volumes reviewed:

Volume	Contents
2.1	Index Volume
2.23	Chemical Warfare Agent References
2.24	Original Urushiol Study
2.25	Heat Exchange/Face Mask Study
2.26	Polymer Fume Fever Review; Study Report on Rescoring of Urushiol Study
2.37	Irritancy/Photoallergenicity/ Contact Sensitization Study
2.39-2.40	Methyl Nicotinate Under Sweating Conditions Study Protocol/ Report

Other documents reviewed:
Meeting minutes from sponsor-Agency interactions
Literature references pertaining to polymer fume fever

2. Table of Contents

3. Chemistry/Manufacturing Controls

See Dr. W. Timmer's Review of Chemistry/Manufacturing Controls Data for more detail.

TSP is composed of a 50%/50% mixture of perfluorinated base oil and PTFE particulates. PFPE and PTFE are inert to nearly all chemicals except ——— and are immiscible in all solvents. PFPE possesses a very low surface energy making it nearly non-wetting to all solvents. PTFE reacts with almost nothing, making it useful in numerous medical devices (e.g., coronary stents, intravenous catheters). The PTFE particles are spherical in shape and have sizes ranging from 0.1 microns to 10 microns, with >90% between 3 and 5 microns. Because they have a corrugated surface with deep crevices, the particles possess a high surface area (about 3 met^2/gram).

By themselves, PFPE or the PTFE particulate exhibit no efficacy as a barrier. The postulated basis of anti-penetration by TSP is 3-fold: (a) immiscibility with all but ———solvents; (b) non-wettability (i.e., substances form droplets on the surface, where they can be wicked away by the overlying garment(s); and (c) barrier-limited diffusion (permeants have a larger mean free path to travel as they diffuse through the TSP, because of frequenct collisions with high surface area PTFE particles).

At the first stage of drug development, a laboratory batch (——— in size) was manufactured at ——— Preclinical lots (——— in size) and clinical lots (——— in size) were prepared at ——— ——— All batches had the same formulation. Human studies were performed with the clinical lots. No human studies have been performed with the scale-up lots.

Pilot Scale-up Lots and Scale-Up Lots (——— in size) were prepared at the McKeeson BioServices. To ascertain that the McKeeson's scale-up batches have the same properties and qualities as those clinical batches for the ——— ——— the Army had ——— conduct an independent evaluation of these lots for their physico-chemical properties. In non-clinical efficacy studies, the barrier properties of the clinical lots were compared with the scale-up lots (see under Animal Pharmacology/Toxicology).

4. Chemical Warfare Agents/Biological Warfare Agents

A consideration of the properties of the different chemical and biological warfare agents against which TSP is designed to function as a percutaneous barrier is necessary before non-clinical and clinical efficacy studies can be interpreted. Accordingly, this section of the review briefly describes the chemistry and toxicity of potential chemical warfare agents (CWA) and biological warfare agents (BWA). Chemical agents can be dispersed by explosive shells, rockets, missiles, aircraft bombs, mines, and spray devices. The agents may be dispersed as a spray, aerosol, or gas, and any of these routes can

potentially result in the contamination of exposed skin surfaces. Individuals not wearing face masks can also be contaminated through breathing the aerosol or gas. Some agents persist on the surface of inanimate objects in the field of exposure (e.g., tree branches) and can subsequently contaminate the skin of individuals who brush against the contaminated objects.

The following table (from Vol. 2.1, pg. 120 of the NDA submission) details the types and characteristics of some chemical and biological warfare agents, as well as that of other permeants.

			Entrance		
Type of Agent	Name	Chemistry	Vapor/ Aerosol	Liquid	Skin Toxicity (LD_{50}, mg/Kg Rabbit)
Nerve	G-Agents (e.g., GA, GD, TGD)	MW range 140-182; GB is miscible in water, GA, GD are water-soluble	Eyes, Lungs	Eyes, Skin, Mouth	[redacted]
	V-Agents (e.g., VX)	MW 267; Soluble in water	Eyes, Lungs	Eyes, Skin, Mouth	[redacted]
Blister	HD	MW 159; Sparingly soluble in water, soluble in most organic solvents	Eyes, Skin, Lungs	Eyes, Skin	[redacted]
Irritant	CS	MW 189; Sparingly soluble in water, soluble in acetone, methylene chloride	Lungs	Eyes, Skin, Mouth	[redacted]
Necrosis	T-2 Mycotoxin	MW 332; Sparingly soluble in water, soluble in most organic solvents	N.A.	N.A.	[redacted]
Other Permeants	Urushiol	MW range 317-363; Soluble in alcohol, ether, benzene			
	Methyl Nicotinate	MW 152; Slightly soluble in water, soluble in ether and chloroform			
From: Vol. 2.23, page 115					

Nerve Agents

Liquid nerve agents penetrate ordinary clothing rapidly. Nerve agents are potentially lethal either through dermal absorption or inhalation. The estimated LD_{50} for a 70 kg human following percutaneous absorption of VX is 10 mg (a single drop). A common feature of nerve agents is that they bind to and irreversibly inhibit the cholinesterase enzymes, which mediate the hydrolysis of the chemical neurotransmitter acetylcholine. This inhibition causes an accumulation of acetylcholine at cholinergic synapses, thus disrupting the normal transmission of nerve impulses at acetylcholine's various sites of action. Death is caused by anoxia resulting from a combination of pharyngeal muscle collapse, increased respiratory secretions, bronchoconstriction, weakness of the muscles of respiration, and central depression of respiration. While all these factors exert an influence on mortality, it is believed that central respiratory depression may be the major

cause of respiratory failure. Thickened soman (TGD) has a thickening agent which is used to decrease the volatility of soman, thereby increasing its persistence in the environment.

Blister Agents

HD can cause injuries to the eye, respiratory tract, and skin. Exposure of skin to a large dose of HD often results in an area of coagulative necrosis surrounded by smaller blisters. The rupture of these blisters increases the risk of secondary bacterial infection. The warm moist skin of the groin area, axillae, antecubital fossae, and neck are particularly susceptible to HD (in people not wearing protective clothing).

Irritant Agents

CS (tear gas) is a reactive chemical irritant that causes dermal irritation. The face, elbows, knees, and groin area are particularly susceptible. The irritation persists approximately one day after exposure.

Necrosis Agents

Systemically absorbed T-2 mycotoxin causes multi-organ effects including emesis and diarrhea, weight loss, nervous disorders, cardiovascular alterations, immunodepression, skin necrosis, and bone marrow damage. Following cutaneous exposure, erythema, tenderness, folliculitis, vesiculation, or petechiae may result, culminating in cutaneous necrosis.

5. Animal Pharmacology/Toxicology

See Dr. L. Reid's Review of Pharmacology and Toxicology Data for more detail. Her review was the source of information for assessing the in vitro and animal efficacy data.

In conjunction with animal and human efficacy experiments (see below), sponsor conducted in vitro analyses of the barrier effect of TSP. The protocol for these analyses (protocol #MREF V-001-01) specified that 0.15 mm thick ——— labeling tape was perforated with 2-cm diameter holes. The tape was then placed on a strip of ——— M8 Chemical Detection Paper (which is used to detect and identify liquid V- and G-type nerve agents and H-type blister agents), and the resulting wells were filled with 100 microliters of either PEG 540 or TSP. A small spatula was used to spread TSP into all regions of the well. One end of a glass microscope slide was dragged across the top of the well to make the TSP surface flush with the top of the ——— labeling tape. Contact of M8 chemical paper with HD results in an easily detectible color change.

Using this in vitro assay, the following studies were performed:

- The pilot batches (study 3.2), the clinical batches (study 3.3), and the scale-up batches (study 3.5) of TSP were tested following protocol MREF V-001-01, with HD challenge commencing one hour after test site preparation. All tested pilot batches and clinical batches (and 7 of 9 assays performed on the scale-up batches) exhibited no breakthrough after a six hour challenge with 8 microliters of HD, while the HD applied to the PEG 540 sites causes an immediate color change on M8 chemical paper.

Reviewer's Comment: These results suggest that pilot, clinical and scale-up batches all retain the property of serving as a barrier against HD penetration to the M8 paper.

- In study 3.4, two U.S. Army issue sunscreens (ICD 2946 and ICD 2947) were tested alone and in combination with TSP 0.015 ml/cm^2 (batch not identified) pretreatment using the M8 chemical paper assay. M8 paper breakthrough times were less than 0.5 minutes with the sunscreens alone, more than 6 hours with TSP alone, and more than 6 hours with sunscreens combined with TSP.

Reviewer's Comment: These results suggest that the two tested sunscreens do not interfere with TSP serving as a barrier against HD penetration to the M8 paper.

- In study 3.5, TSP produced in scale-up batches applied as little as 5 minutes before HD was applied, or as much as 24 hours before HD was applied, prevented breakthrough of HD to the M8 paper for 6 hours.

Reviewer's Comment: These results suggest that in the in vitro assay, the amount of time elapsing between TSP application and challenge does not affect breakthrough time. It is not clear whether these results can be extrapolated to the in vivo situation.

- In study 3.5, 25 microliters of 6.25 micrograms/cm^2 or 62.5 micrograms/cm^2 of permethrin in isopropanol was applied onto the TSP and allowed to dry before the 8 microliter challenge of HD was applied. In two of the assays involving the higher permethrin concentration (but none of the assays involving the lower permethrin concentration), HD broke through the TSP barrier in less than 6 hours.

Reviewer's Comment: These results suggest that high concentrations of permethrin may abrogate the barrier property of TSP.

The Pharmacology/Toxicology data submitted by sponsor addresses the separate issues of (1) characterizing the toxicologic profile of TSP and (2) characterizing the degree of protection TSP provides from subsequent exposure to chemical warfare agents (CWA) in "animal efficacy experiments". Since the latter issue can only be addressed directly in an ethical manner in laboratory animals and not in humans, it is necessary to extrapolate from the results observed in laboratory animals to the anticipated degree of protection in humans. This approach has the regulatory precedent of a Federal Register notice published October 5, 1999 entitled "Evidence Needed to Demonstrate Efficacy of New Drugs for Use Against Lethal or Permanently Disabling Toxic Substances When Efficacy Studies in Humans Ethically Cannot Be Conducted". In this notice, Agency proposed 4 criteria to be used in approving new drug or biologic products that are intended to reduce or prevent serious or life-threatening conditions based on evidence of effectiveness derived from animal studies, without adequate and well-controlled efficacy studies in humans: (1) "there is a reasonably well understood pathophysiological mechanism for the toxicity of the...substance and its amelioration or prevention by the product; (2) the effect is independently substantiated in multiple animal species...; (3) the animal study endpoint is clearly related to the desired benefit in humans...; and (4) the data or information on the kinetics and pharmacodynamics of the product...allows selection of an appropriate dose in humans."

Sponsor conducted animal efficacy experiments testing TSP's ability to protect against a variety of CWA/BWA. Vesicant agents and T-2 mycotoxin act locally at the skin surface to induce blistering/necrosis and folliculitis/necrosis, respectively. The endpoint in

animal efficacy experiments was to determine whether TSP delayed or reduced percutaneous penetration of these agents, as measured by reduced lesion area or severity. Extrapolation of these results to human outcomes is problematic because there is no available published literature which compares the dose response relationship of HD in animals and humans. It cannot necessarily be assumed that the dose response relationship between animals and humans would be identical because there are inherent differences in a variety of anatomic and physiologic features of human and rabbit skin (e.g., thickness, hair follicle density). A dose of HD that penetrates TSP but is "subclinical" on rabbit skin would not necessarily be "subclinical" in human skin. Thus, it cannot be inferred from a finding of "complete protection" in rabbits skin that humans would be "completely protected".

For characterization of protection from nerve agents, sponsor relied upon measurement of protection from nerve agent-induced lethality by TSP, as well as measurement of protection from decrease in whole blood and red blood cell acetylcholinesterase activity. What is the clinical significance to humans of a decrease in plasma and acetylcholinesterase activity, given that depression of CNS acetylcholinesterase (AchE) activity is presumed to be the mechanism of death? There is no published literature addressing this question in humans, and it would not be ethically feasible to perform the type of studies needed to answer this question.

Wolfe et al. (Toxicol. and Appl. Pharmacol. 117: 189-193, 1992) endeavored to address this question in rhesus monkeys, by infusing monkeys with purified cholinesterase before exposure to soman. The rationale for this approach was that if soman acts toxicologically by inhibiting brain AChE, then large quantities of exogenously added cholinesterases in the blood would sequester the soman before it reaches its physiologic target. Monkeys were infused with a dose of cholinesterase calculated to be sufficient to neutralize *in vitro* 5 LD_{50} doses of soman. Monkeys pretreated in this manner were able to tolerate up to 5 LD_{50} doses of soman, administered in 3 discrete steps, with no lethality, and with no or minimal effect on neurological performance. Blood cholinesterase levels measured before and after each soman challenge showed a linear decline with increasing soman dose. The authors concluded that the strong linear relationship between soman dose and residual cholinesterase level confirmed their hypothesis that stoichiometric reaction was responsible for the observed protection. "Soman was sequestered by exogenous and endogenous ChEs in the blood before it could reach physiologically critical target AChE."

Carbamate pretreatment in combination with atropine constitutes a therapy which can be effective against poisoning from soman in laboratory animals and humans. The hypothesized mechanism of action of carbamate is to reversibly inhibit a portion of tissue AchE, thereby preventing irreversible inactivation by soman. Lennox et al. (Life Sciences; 37, 793-795; 1975) conducted a study in rats and guinea pigs to determine the correlation between reversible inhibition of whole blood AChE activity and efficacy against soman-induced lethality. These researchers concluded that inhibition (i.e., protection) levels as low as 10% of the initial whole blood cholinesterase level provided

some degree of protection against soman-induced lethality in rats and guinea pigs, with the degree of protection more pronounced in guinea pigs than in rats.
Based on these published results from a variety of animal species, a reasonable criteria for relevant TSP-mediated protection **of animals** would be if TSP prevents AChE levels from falling close to zero. A reasonable working hypothesis by which to extrapolate the animal efficacy data to predict human protection is that if TSP were to prevent reduction of human whole blood acetylcholinesterase activity below 10% of initial levels, then it may increase the probability of humans surviving a dose of nerve agent in conjunction with other interventions (i.e., rapid evacuation from the site of exposure, removal of contaminated clothing and decontamination of skin, administration of atropine and carbamates). However, it is unknown whether the results from animal efficacy experiments can be directly extrapolated to human outcomes. It is noteworthy that there is no direct previous human experience available either in support or in refutation of this hypothesis. It is theoretically possible that differences in the relative sensitivities of human and animal whole blood and CNS acetylcholinesterases, or differences in the permeability of human and animal blood-brain barriers to nerve agents, may mean that animals could survive a reduction to 10% whole blood cholinesterase levels, but in humans a reduction to 10% whole blood cholinesterase levels is associated with death.

Animal Efficacy Data

The following is not a complete or comprehensive survey of the results from the animal efficacy studies; Dr. Reid's review contains such a survey. Rather, it is a focused survey of those animal efficacy study results from which (cautious) extrapolation to human protection may be possible. Of note, animals that died during the course of these studies were assumed to have less than 10% baseline AchE levels.

In study 3.6, a 0.1 mm thick layer of TSP was applied to the clipped dorsa of anesthetized rabbits. One hour later, droplets of VX [0.5 mg/kg (10-20 LD_{50} dose)], or of TGD (thickened soman) [3.35 mg/kg (1 LD_{50} dose)], or 1 microliter of HD were applied to the TSP-treated skin sites on the rabbits (no animal was exposed to more than one CWA). Control animals were exposed to the same volume of the CWA, without TSP pretreatment.

- Mean HD-induced lesion sizes were 3.5 fold smaller at TSP-protected sites.
- TGD:
  - Unprotected animals: Percentage retained AchE levels ranged from 12-137% of baseline at one hour after exposure, ranged from 7-90% at 24 hours after exposure.
  - Protected animals: Percentage retained AchE levels ranged from 28-118% of baseline at one hour after exposure, ranged from 0-116% at 24 hours after exposure.
- VX:
  - Unprotected animals: Percentage retained AchE levels ranged from 4-135% of baseline at one hour after exposure, ranged from 0-33% of baseline at 24 hours after exposure.

- Protected animals: Percentage retained AchE levels ranged from 6-121% of baseline at one hour after exposure, ranged from 20-115% of baseline at 24 hours after exposure.
- No unprotected or protected animals in "danger zone" (<10% AchE level) at half-hour after exposure.

In study 3.7, the barrier properties of TSP against penetration of HD vapor were compared against unprotected exposed sites on the backs of anesthetized hairless guinea pigs. TSP was applied to a thickness of 0.2 mm onto sites on the dorsa of guinea pigs. Fifteen minutes after TSP application, the animals were exposed to HD vapor. The vapor was kept in contact with the sites using 12 mm diameter plastic vial caps inverted onto each site. The estimated concentration of HD vapor within the plastic caps was 1.4 mg/L (the equilibrium concentration of HD vapor at 30°C). The duration of exposure to HD vapor ranged from 4 minutes to 20 minutes.

- TSP decreased erythema compared to untreated sites at 5, 10 minutes after challenge, but no protection was observed at 15 minutes or later after challenge.

In studies 3.8, 3.9, 3.14 and 3.15, TSP was applied to rabbit skin. One hour after application, the animals were challenged with one microliter of HD liquid (3.8, 3.9, 3.14) or 2 microliters T-2 mycotoxin (3.15). After 4 hours, the HD treated sites were decontaminated. At 1, 2, 4, and 6 hours, the T-2 mycotoxin treated sites were decontaminated.

- HD-induced lesions sizes were approximately 80% smaller than unprotected control sites.
- TSP protected sites from T-2 mycotoxin for up to 6 hours after exposure.

In studies 3.12 and 3.13, TSP was applied to rabbit skin. One hour after application, the animals were challenged with direct application of liquid VX (10 LD_{50} dose) or TGD (1 LD_{50} dose) to the site that had been pretreated with TSP (in study 3.13, GD was substituted for TGD).

- Study 3.12: At one hour after exposure, all 24 TSP-protected animals challenged with TGD, and 23/24 TSP-protected animals challenged with VX retained more than 10% of baseline RBC AchE levels. By four hours after exposure, 7/24 VX-challenged TSP-protected animals retained less than 10% of their baseline AchE levels. Virtually all control (unprotected) rabbits had >90% loss in AchE activity by 4 hours after challenge.
- Study 3.13: At one hour after exposure, 20% of VX-challenged TSP-protected animals (and 12% of GD-challenged TSP-protected animals) had less than 10% of baseline whole blood AchE levels. By four hours after exposure, 42% of VX-challenged TSP-protected animals (and 12% of GD-challenged TSP-protected animals) had less than 10% of baseline whole blood AchE levels. 86% of GD-challenged, unprotected animals and 100% of VX-challenged, unprotected animals were dead at 4 hours after challenge.

- Exposures to GD resulted in some reduction in whole blood AchE levels in over 99% of animals, while exposures to VX resulted in reductions in whole blood AchE activity in only 67% of the animals, with the remaining animals retaining 100% activity over the 4 hour challenge activity.

In study 3.16, TSP was applied to clipped rabbit skin to a thickness of 0.15 mm. Fifteen minutes after application, ——— Chambers were loaded with 0.1 ml of 1.0% CS dissolved in trioctylphosphate. The ——— Chambers remained in contact with the skin sites for 15 minutes. After the exposure period, the chamber was removed and the site decontaminated, removing both the CWA and the TSP. Sites were scored for dermal irritation at 15, 30, 60, 120, 240 minutes and at 24 hours after exposure.

- 9/20 unprotected sites developed erythema within 15 minutes after challenge, while 1/20 TSP-protected sites devloped erythema within 15 minutes after challenge. At 4 hours after exposure, all unprotected sites were erythematous, but only 6/20 protected sites were erythematous.

In study 3.17, TSP was applied to rabbit skin with subsequent application (after one hour for TSP to set) of either DEET(US Army Medical Material No. IXDM) or of different types of camouflage paint. These sites were then challenged with 4 hours of continuous exposure to a one microliter droplet of HD applied from a micropipet. In study 3.18, DEET was applied to rabbit skin and wiped off (either with dry gauze or a moist towelette) after a 3 hour wear period, or applied and left undisturbed. Four hours after moist wiping, or 3 hours after dry wiping, TSP was applied on top of these sites, which were then challenged with HD.

- Lesion size increased when insect repellant, loam camouflage paint, and sand camouflage paint was applied on top of TSP.
- DEET pre-treatment largely abrogated TSP protection from HD (lesion size became the same as unprotected controls), even if DEET was subsequently removed with a moist towelette. Dry gauze removal of DEET, followed by TSP application and HD challenge, reduced lesion size by half compared to unprotected controls.

*Reviewer's Comment: In the battlefield setting, it is more likely that camouflage paint would be applied **before** TSP was applied. The results from Study 3.18 do not address whether the barrier properties of TSP are preserved if TSP is applied on top of these camouflage paints.*

Study 3.19 was performed to test whether DEET interferes with protection from VX if DEET is applied prior to the TSP. Clipped rabbit back skin was treated with 2 applications of liquid DEET (1.9 microliter/cm^2), administered on the day prior to and approximately 3 hours prior to pretreatment with TSP. One hour after TSP application (4 hours after the last application of DEET), a liquid challenge of VX (10 LD_{50} dose) was applied to the TSP treated sites.

- At four hours after VX challenge, all unprotected animals were dead. More than two-thirds of TSP-protected animals, with or without DEET pretreatment, retained more

than 10% baseline RBC AchE activity at one hour after challenge. At 4 hours after challenge, 30% of TSP-protected animals had less than 10% residual RBC AchE activity, and 63% of DEET-treated and TSP-protected animals had less than 10% residual RBC AchE activity.

The following conclusions and inferences are drawn from the set of animal efficacy data:

- TSP is a barrier, compared to unprotected controls, for a variety of CWA/BWA, including HD, T-2 mycotoxin, CS, CR, TGD, GD, and VX.
- At early time points after CWA/BWA challenge, for the majority of TSP-protected animals, a small enough amount of percutaneous penetration has occurred so that if those animals were decontaminated and treated with antidotes for CWA/BWA at those early time points, the likelihood of serious morbidity or mortality would be minimal. The time window before significant percutaneous penetration occurs is dependent on the particular experimental conditions, including the type and amount of agent, and ranges from 0.5 hours to 1 hour.
- At late time points (from 4 to 6 hours after challenge, depending upon the experimental conditions), a large enough amount of percutaneous penetration has occurred so that substantial numbers of TSP-protected animals would suffer serious morbidity or mortality, even with subsequent decontamination. At all time points, TSP-protected animals would be predicted to fare better than if they had been unprotected (i.e., TSP does not merely delay morbidity/mortality, but appears to partially prevent it, for the duration of the experiment). This interpretation is limited by the consideration that challenge was not permitted to extend beyond 6 hours in any animal efficacy experiment
- Treatment with DEET before or after TSP application interferes with TSP-mediated protection, but does not completely abrogate the protection. Insect repellant and some camouflage paints, when applied after TSP, partially abrogate TSP-mediated protection.

Reviewer's Comment: It is noteworthy that in most described animal efficacy experiments, at least one hour elapsed between TSP application and challenge with permeant. It is not clear whether it can be extrapolated from these data that TSP would be as efficacious at blocking CWA if less than an hour elapsed between application and challenge. In addition, a steel spatula was used to spread uniformly the TSP prior to challenge. It is not clear whether spreading with fingertips, which may give a TSP coat with less uniform thickness, would be as efficacious as spreading with a steel spatula.

5. Human Pharmacokinetics/Pharmacodynamics

See Dr. Bashaw's Review of Human Pharmacokinetics Data. The Biopharmaceutics Review was not available at the time the medical review was completed.

Sponsor performed a study (Vol. 2.23, pg. 187-215) of the penetration and substantivity properties of PFPE when it is applied to the volar forearm skin of normal human volunteers. Substantivity and penetration were measured with surface attentuated IR absorption spectroscopy, via detection of relevant IR absorption bands.

Ten healthy volunteers refrained from applying lotions, creams, oils, or other topical agents to their forearms for 48 hours before the study started. Surface IR scans were performed on 10 cm^2 sites (2 sites/arm). Twenty-five microliters of PFPE were applied randomly to one site on each forearm (sponsor does not specify how the PFPE was applied). The remaining site on each forearm served as an untreated control.

One hour after application, treated and control sites on one of the arms were scanned and IR absorption was measured. Both sites were scanned at surface and at layers exposed by 5, 10, and 15 tape strippings. The contralateral arm was then serially washed by spraying a 4% solution of castile soap on both sites, rinsing with distilled water, and repeating the washing procedure twice. After 30 minutes of air drying, the sites on the washed arm were also scanned and IR absorption was measured.

Sponsor concluded that PFPE penetrated the stratum corneum to at least a depth of 10 serially stripped layers, with the product reaching a depth of 15 layers in most cases. The fraction of PFPE remaining after the washing (i.e., the substantivity) was 46%.

6. Human Clinical Experience

Foreign Experience

TSP has not been approved for marketing in any country.

Clinical Studies

Introduction

It is noteworthy that no clinical studies have been submitted in this application in which TSP is used under the proposed conditions of labeling. The clinical efficacy studies that have been submitted use two cutaneous sensitizing agents (Rhus antigen and methyl nicotinate) as CWA surrogates. The studies were performed under controlled laboratory conditions and do not mimic the field conditions for application and use of TSP. The differences between the controlled laboratory conditions and expected field conditions are detailed in the relevant sections of this review.

In the event of CWA or BWA attack, or if there is suspicion of such an attack, upon U.S. armed forces personnel, personnel have been equipped with and trained to use MOPP (mission oriented protective posture) gear, which consists of protective overgarment, mask with hood, overboots, and gloves. One shortcoming of MOPP gear is that CWA/BWA may potentially gain access to and contact skin directly at the junctures of these protective garments (i.e., boot tops, waist, wrists, neck). In addition to these potentially susceptible sites, sponsor has determined that moist, warm body sites such as axillae and groin need extra protection because some CWA (e.g., HD) preferentially solubilize in warm, moist areas.

The mechanisms by which TSP is believed to interfere with percutaneous penetration of permeants such as CWA and BWA are three-fold: (1) because TSP components are hydrophobic and lipophobic, potential permeants would not solubilize easily in the paste,

remaining instead above the TSP layer; (2) because TSP is non-wettable, potential permeants would remain "beaded up" on top of the TSP layer, where the overlying garments could soak up the permeant; and (3) the presence of PTFE particles in the TSP would increase the mean free path length of permeants through the TSP. TSP may both prevent penetration and prolong penetration.

The Sponsor has not submitted clinical efficacy studies in which the barrier properties of TSP are tested under conditions which closely simulate what would be experienced by individuals who use the TSP in the battlefield (or under the proposed conditions of labeling, i.e. "in conjunction with appropriate chemical protective clothing"). The clinical efficacy studies were performed under controlled laboratory conditions, without battle dress uniform or MOPP gear worn over the TSP layer. It is possible that under battlefield conditions, rubbing by overlying garments may compromise the TSP barrier. In addition, the clinical efficacy studies submitted in support of this NDA use two cutaneous sensitizing agents (urushiol and methyl nicotinate) as surrogates for CWA. Because CWA/BWA differ from urushiol and methyl nicotinate with respect to their chemical and physical properties, TSP may not necessarily be as impervious a barrier to CWA/BWA as to urushiol and methyl nicotinate.

The source of information concerning the toxicity of chemical warfare agents is "Treatment of Chemical Agent Casualties and Conventional Military Chemical Injuries", Army FM 8-285 Field Manual, Vol. 2.23 of NDA submission, pg. 002-057.

With respect to nerve agents, the scenario which TSP is designed to interrupt is one in which percutaneous penetration occurs, followed by systemic exposure through hematogenous spread. One manifestation of systemic exposure to nerve agents is inhibition of red blood cell or whole blood acetylcholinesterase activity. There is no published literature that correlates in humans the lethality associated with nerve agents and the degree of red blood cell or whole blood acetylcholinesterase activity. Such a study is not ethically feasible.

Blister agents are used to degrade fighting efficiency rather than to kill, in that they burn and blister the skin or any other part of the body they contact. The scenario which TSP is designed to interrupt is one in which percutaneous penetration occurs, followed by local action. The severity of a blister agent burn is directly related to the concentration of the agent and the duration of contact with the skin.

The U.S. Armed Forces Field Manual (Army FM 8-285), entitled "Treatment of Chemical Agent Casualties and Conventional Military Chemical Injuries", details the specific conditions under which military personnel are expected to put on MOPP 4 gear. It also details the steps that personnel must undertake if they or their buddy experiences contamination of the eyes or skin with vesicants or nerve agents. Self aid consists of individual decontamination and administration of chemical agent antidotes. Buddy aid may entail masking the casualty, administering antidoes, administering assisted ventilation, decontaminating the casualty, putting on protective clothing to prevent further contamination, and evacuating the casualty as soon as possible.

The following table lists all human studies submitted in NDA 21-084, with enrollment numbers and number of exposures per study.

Study No.	Design	No. of Enrolled Patients Exposed to TSP	Extent of Exposure	Outcome
	Pharmacokinetics Study			
A6704	Dermal Irritancy	22	Single exposure	No evidence of dermal irritancy
A6705	Dermal Contact Sensitization/ Photosensitization	20	Six exposures over 37 days	No evidence of dermal contact sensitization or photosensitization
	Protection Against Rhus Sensitization	50	One exposure	TSP protects against Rhus sensitization
A-8522	Protection Against Methyl nicotinate Irritation	59	One or two exposures	TSP protects against Methyl nicotinate irritation
Log No. TPMD95004-AP019-H018	Heat Exchange Study	10	One exposure	TSP does not interfere with heat exchange
A6786	Mask Fitting Study	42	One exposure	TSP does not interfere with protective mask fit
	Penetration/ Substantivity Study			

Including all human studies, fewer than 300 individuals have been exposed to TSP. The majority of people exposed to TSP had a single exposure. Most patients had a relatively small percentage of body surface area exposed.

This is a comparatively small database from which to assess TSP safety, but because human pharmacokinetics studies suggest that TSP is not able to penetrate the stratum corneum, there is less basis for concern that systemic adverse effects might ensue from topical application of TSP.

6.1 Dermal Toxicity Studies

All dermal toxicity studies were performed with the final to-be-marketed formulation, consisting of a 50%/50% mixture of PTFE particulates suspended in PFPE oil.

Dermal Irritancy Study
Protocol Number: Log No. A6704

Study Title: "An Assessment of the Irritancy Potential of a Candidate Topical Skin Protectant"
Study Date: March –April, 1995
Study Location: Miami, Fl
Investigators: Principal Investigator: Kenneth C. Lasseter, M.D.
Barry I. Resnick, M.D.

NUMBER OF SUBJECTS: 22 enrolled, 20 completed study

AGES OF SUBJECTS: 18-35 years old (mean age of subjects who completed study was 27.0 years, with a standard deviation of 5.2 years)

INCLUSION CRITERIA:

- Male or female subjects between 18 and 35 years of age.
- Subjects with no chronic dermatological condition, no photo-sensitive inherited or acquired diseases nor atopic background by baseline medical history.
- Subjects to be available for the time period the study would encompass.

EXCLUSION CRITERIA:

- Subjects with cutaneous or systemic diseases as manifested by clinically significant abnormalities of screening tests.
- Subjects with a history of atopy (asthma, eczema or hay fever) or a history of chromic dermatological diseases and/or acute dermatological disease.
- Volunteers with a history of allergic reactions to glycols or other cosmetics and/or skin care products.
- Subjects were required to have no history of cortisone injections or oral cortisone use for at least 1 month prior to the study. Subjects were also required to be free of any other medication which has been associated with photosensitivity reactions or any medication which interferes with potential inflammatory and/or immunologic responses caused by the test material.
- Subjects with a hisory of inherited or acquired photosensitivity disease (e.g., porphyria, lupus erythematosus).
- Subjects with a history of immediate urticarial type disease.
- Subjects with exposure of the back to sun within the last week or have had a sunburn within the past month.
- Pregnant females.
- Any male or female who is markedly overweight or underweight or who is not able or unwilling to comply with the specific instructions regarding bathing and care of the test sites or who is unwilling to have the marking material applied to the testing site.

STUDY OBJECTIVE/DESIGN:
To determine the cutaneous irritancy and photo irritancy potential of the TSP in healthy male and female volunteers.

SOURCE OF STUDY MATERIALS:
— chambers were obtained from ——— The ultraviolet irradiator which was utilized in this study (model — is a xenon arc lamp obtained from ——— with an emission spectra from 290 to 400 nm. The TSP (— — Lot No. 305 — 794) was provided in a bulk bottle by ———

STUDY PLAN:
Overview: This was an open label single exposure study of the irritancy produced by TSP alone or combined with ultra-violet irradiation.
Day 1: Four — patches applied to back of subjects: two patches contained 50 mg TSP, two patches served as controls. A test site on the buttocks was irradiated with 10J/cm^2 UVA light.
Day 2: Patches removed and assessed. UVA-irradiated test site assessed. Because none of the subjects had a reaction to the test ultra-violet irradiation, two of the patches (1 TSP and 1 control) were irradiated with 10 J/cm^2 UVA light.
Days 4 and 6: Test sites were evaluated.

Primary Efficacy Variables:
Test sites were evaluated using the North American Contact Dermatitis Group Scoring System as follows:

1	Weak (nonvesicluar) reaction: erythema, infiltration, possibly papules (+)
2	Strong (edematous or vesicular) reaction (++)
3	Extreme (spreading, bullous ulcerative) (+++)
4	Macular erythema only (+/-)
5	Irritant morphology (glazed, burned, pustular ulcerative) reaction
6	Negative reaction (-)
7	Not tested

Clinical Endpoints: Day 6 of the clinical study.

Safety Results:
Non-directed questioning regarding symptoms for evaluating clinical adverse experiences. Each subject was also given a complete physical examination at the end of the study. All patients were asymptomatic, and there were no findings on physical examination.

Reactivity Results:
On both days 4 and 6, all sites (photo-tested or non-photo-tested, placebo or active treatment) had negative reactions.

CONCLUSIONS:
Since the two components of TSP are chemically inert and do not absorb UV radiation, the observed results that TSP is non-irritating and not photo-irritating are consistent with expectations. The observation that acute application is non-irritating is extended in the following studies, where 3 weeks of TSP application, as part of the dermal contact sensitization study, is also non-irritating.

Dermal Contact Sensitization/Photosensitization Study

Protocol Number: Log No. A6705

Title: An Assessment of the Contact Sensitization and Contact Photo Allergic Potentials of a Topical Skin Protectant (TSP)
Study Date: April--May, 1995
Study Location: Miami, Fl.
Investigators: Kenneth C. Lasseter, M.D.
Barry I. Resnik, M.D.

NUMBER OF SUBJECTS: 20 (19 subjects evaluated)

AGES OF SUBJECTS: 18-45 years old

INCLUSION CRITERIA:
- Male or female subjects between 18 and 45 years of age.
- Other inclusion criteria identical to those in the dermal irritancy study.

EXCLUSION CRITERIA:
- Identical to the exclusion criteria in the dermal irritancy study

STUDY OBJECTIVE/DESIGN:
To determine the contact sensitization and contact photoallergy potential of TSP.

SOURCE OF STUDY MATERIALS:
[redacted]chambers were obtained from [redacted]. The ultraviolet irradiator which was utilized in this study (model [redacted] was obtained from the [redacted]. The ultraviolet irradiator which was utilized in this study (model [redacted] is a xenon arc lamp obtained from the [redacted] with an emission spectra from 290 to 400 nm. The TSP ([redacted] Lot No. 305 [redacted] 794) was provided in a bulk bottle by [redacted]

STUDY PLAN:
Overview:
This was an open label multiple exposure study of the potential for contact sensitization and contact photoallergy produced by TSP alone or combined with ultra-violet irradiation.

Induction Phase
Day 1: Four — patches were applied to deltoids of subjects: two patches were controls, two patches contained sodium lauryl sulphate (SLS). A test site on the buttocks was irradiated with 10J/cm^2 UVA light.
Day 2: The irradiated site was checked for the presence of erythema (no subjects had erythema at the test site). Four — patches were applied to the deltoids of subjects: two patches contained TSP and two patches were controls. The patches were placed so that the areas that had been exposed to SLS were subsequently exposed to TSP.
Day 4: Patch sites were checked for reactivity. Two of the patch sites (exposed to SLS/TSP, or control/control) were irradiated with 10J/cm^2 UVA light. Patches containing SLS were reapplied to the SLS/TSP exposed patch sites; control patches were reapplied to the other two (control) sites.
Day 5-7, 8-10, 11-13, 14-16: Actions performed on Days 2-4 were repeated.
Challenge Phase
Day 35: Four — patches applied to backs of the nineteen subjects: two patches contained TSP, two patches were control patches. (One subject (#11) reported for the challenge phase on Day 36. For this subject, the challenge phase was shortened, so that the final evaluations were performed at 72 hours.)
Day 37: All subjects returned at 48 hours post-patch application, at which time the patches were removed and all four sites were assessed for reactions. Two of the patch sites (1 TSP and 1 control) were irradiated with UVA.
Days 39: The subjects returned for re-evaluation of the sites.

Primary Efficacy Variables:
Test sites were evaluated using the North American Contact Dermatitis Group Scoring System (identical to the scoring system that was employed in the dermal irritancy study)

Clinical Endpoints: Day 39 of the clinical study

Safety Results:
Non-directed questioning regarding symptoms for evaluating clinical adverse experiences. Each subject was also given a complete physical examination at the end of the study. All patients were asymptomatic, and there were no findings on physical examination.

Reactivity Results:
During the induction phase, some of the sites exposed to SLS developed doubtful or weak reactions, but these reactions were not intensified following 24 hour exposure to TSP. No subjects were obliged to discontinue their participation due to this irritation.

During the challenge phase, no cutaneous reactions were obtained in response to either photo or contact testing with TSP in any of the nineteen subjects.

CONCLUSIONS:
These results suggest that TSP is safe and well tolerated by healthy normal subjects, both on a contact sensitization basis and under photo-stimulated conditions.

6.2 Human Efficacy Studies

All human efficacy studies were performed with the final to-be-marketed formulation.

Study Title: "An Assessment of the Ability of the Topical Skin Protectant (TSP) to Protect Against Contact Dermatitis to Rhus Antigen"

Study Date: April, 1996- August, 1997
Study Locations: National Naval Medical Center, Bethesda, MD
Investigator: Dennis Vidmar, M.D.
Associate Investigator: David Mezebish, M.D.

Objective/Rationale:
The objective of this Phase 2 clinical trial was to assess whether the TSP can prevent experimentally induced allergic contact dermatitis due to rhus antigen (urushiol) in human subjects.

Design:
This was a one study site open (unblinded) investigation. Patients served as their own controls in the study. The study was conducted in two stages: Stage I (screening for urushiol reactivity) and Stage II (testing if TSP blocks urushiol reactivity). The duration of the second stage of this study was 96 hours, and no formal follow-up past this time period was performed. However, because the study volunteers were U.S. armed forces personnel and their dependents, a degree of "informal" follow-up was possible for these subjects that would not have been possible on civilian subjects. (See Adverse Events section). After the clinical study was completed, independent blinded rescoring of the reactivity scores (based on photographs of the reactivity site) was performed.

Source of Study Materials:
The rhus antigen was prepared using acetone extraction techniques, with concentration standardized using HPLC methods. Four different lots of urushiol extract were used in this study, with concentrations of .570, .429, .411, and .623 mg/ml in acetone. Since the primary comparison was between urushiol challenged TSP-treated and TSP-untreated within each subject, and since different urushiol lots were never used on the same subject, knowledge of the comparative potencies of the different urushiol lots is not critical for assessing the relative protection afforded by TSP.

PROTOCOL OVERVIEW:
Population, procedures
83 men and women were enrolled in the protocol. 81 of these enrollees completed Stage I of the protocol (screening for reactivity to urushiol, see below). 51 of the subjects who completed Stage I were found to be reactive to urushiol, and 50 of these subjects progessed to Stage II (testing whether TSP blocks rhus dermatitis). Two of these subjects did not react at the unprotected sites within 96 hours after Rhus application, and their results were not included in the efficacy analysis.

Subject ages ranged from 18 to 44 years old.

INCLUSION CRITERIA

- Subjects were male and female, unrestricted as to race or ethnicity, between 18 – 45 years of age, and in good general health as established through a medical examination.
- Subjects should describe a history of reactions suspicious for poison ivy/poison oak dermatitis.

EXCLUSION CRITERIA

- Subjects should not be knowingly pregnant or HIV antibody positive.
- Subjects should have no significant chronic dermatologic conditions, or an atopic background by medical history. Subjects shuold have no active significant dermatolgic disease as determined by dermatologic examination.
- Subjects should not have a history of allergic reaction to glycols or cosmetics and/or skin care products.
- Subjects should have no history of coritsone injections or oral cortisone use or oral antihistamine use for at least one month prior to testing.
- Subjects should not have used topical corticosteroids on the area to be tested (upper arms and forearms) for at least 2 weeks prior to testing.
- Subjects should not have exposed their forearms to sunlight to the point of redness over the past week, or have had a sunburn anywhere on the body within the last month.
- Subjects should be free of any medication which interferes with potential inflammatory and/or immunologic responses caused by the test material such as (NSAIDs). for at least 14 days.

Protocol Synopsis
Stage I
Screening (Day #1)
Subjects undergo medical history and concomitant medication review, brief general physical examination, HIV antibody testing.

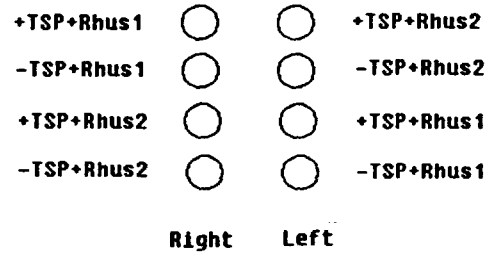
Screening/Rhus Application (Day #4)
Serum pregnancy test were conducted on female test subjects. (No volunteers have test materials applied to their skin until the results of serum pregnancy test are known to be negative).
Open patch tests for rhus antigen were applied to sites on subjects' ventral forearms. Five microliter aliquots of four serial dilutions of urushiol in acetone were applied to four test sites on the ventral forearms. A non-occlusive gauze dressing was taped loosely over the sites.
Four hours later, the subjects returned to clinic, where the test sites were gently cleansed under the supervision of the dermatology clinic staff using Cetaphil® skin cleanser and lukewarm water.

Evaluation of Rhus Antigen Sensitivity (Days #6 and #8)
Test sites were evaluated and graded by both the investigators, utilizing the North American Contact Dermatitis Group scoring system. Only those subjects who demonstrated a 1+ (erythema, infiltration, papules) or greater reaction to a urushiol test dose of 4.75 nmol or less on at least one of the evaluation days were advanced to Stage II of the process.

Stage II (performed not less than 3 days after Stage I; patients who demonstrated a 3+ (spreading, bullous) reaction to more than one stage I site were not advanced to stage II until the dermatitis from Stage I subsided).

Screening (Day #1): identical to Stage I screening

Screening/TSP/Rhus Application (Day #4): Serum pregnancy test were conducted on female test subjects. (No volunteers have test materials applied to their skin until the results of serum pregnancy test are known to be negative).
Five 8 mm circular test sites on both ventral forearms and two 8 mm circular test sites on the inner aspect of one upper arm are drawn with a pre-cut template and a gentian drawing pen. 2 cm circles, centered around the 8 mm circle, were then drawn at these sites using a pre-cut template and a gentian marking pen. Four designated sites on each ventral forearm and two on the upper inner right arm were wiped with 70% (v/v) isopropyl alcohol and allowed to air dry. 100 micrograms of TSP (Lot #306I0794), dispensed by a TB syringe, was applied to two of the test sites on each ventral forearm (see diagram on next page) and one of the sites on the upper inner arm by a trained non investigator and spread uniformly by a stainless steel dental spatula. Thirty to 60 minutes after TSP application, 3 aliquots, 1.7 microliter in volume, (total of 5 microliters) of urushiol in acetone at a concentration that had been demonstrated in Stage I to be sufficient to induce a 1+ reaction in subjects (Rhus1) was applied to the two sites on each forearm (one TSP-protected, one unprotected). A 5 microliter aliquot of urushiol in acetone at a higher concentration (Rhus2) was applied to two sites on each forearm (one TSP-protected, one unprotected). The two sites on the upper right inner arm were treated with 5 microliters of acetone. All the sites were allowed to air dry.



The technician's standard operating procedure states: "Note that the technique [of urushiol application] differs between TSP protected and TSP unprotected sites. TSP unprotected sites should have all 3 aliquots sequentially placed at the center of the inner 8 mm circle. TSP protected sites should have the 3 aliquots placed in a triangular pattern." Diagrams of how the urushiol was to be applied to the TSP unprotected and protected sites are shown below:

TSP Unprotected TSP Protected

Medical reviewer submitted an information request to Sponsor for clarification concerning the reason for why urushiol was applied in different fashion to TSP unprotected and protected sites. Sponsor responded that this difference was necessary because "an aliquot of the challenge liquid in acetone behaved differently on...bare skin...compared with TSP-protected sites. Challenge liquid droplets tended to spread rapidly on bare skin test sites, whereas droplets on top of TSP tended to "bead up" because of the surface properties of the TSP protective layer and the immiscibility of the acetone solution with TSP." Thus, the urushiol challenge was administered in the above described manner to the TSP unprotected sites "to minimize the probability that the challenge droplet would spread beyond the boundary of the test site." Sponsor further notes that "in administering the three 1.7 microliter aliquots on top of the TSP, it was observed that they coalesced in the center of the test site."

Reviewer's Comment: It is unclear what the consequences are of having different methods of application of urushiol to the sites. It would have been preferable for sponsor to apply the urushiol in an identical fashion at all sites to avoid systemic bias stemming from different application protocols.

Small plastic dishes were applied and secured with paper tape over all forearm sites, then the dishes were covered with a loose gauze dressing, to prevent smearing of the applied materials.

Four hours later the subjects returned to clinic to gently cleanse the test sites under the supervision of a trained dermatology clinic staff using Cetaphil® skin cleanser and lukewarm water.
At 48 hours and 96 hours after TSP and rhus application, the subjects returned to clinic so that investigators could examine and score the test sites, using the same scale as described for Stage I. Reactive sites were photographed at 96 hours.

Reviewer's Comment:
The purpose of the 30 minute to 60 minute TSP "wear time" prior to application of urushiol is unclear. Given the intended use of TSP, it seems plausible that battlefield personnel may not always have the luxury of thirty to sixty minutes' notice of impending chemical or biological attack before they apply the TSP. Hence, it is incumbent upon the sponsor to test TSP efficacy under more realistic conditions (i.e., immediately after TSP application). Since TSP is a viscous suspension that does not contain volatile solvents that would be expected to evaporate following contact with human skin for one hour, no expected change in the physico-chemical characteristics of the TSP would be expected following prolonged exposure to skin.

The necessity of cleansing the skin with isopropyl alcohol and letting it air dry for effective application of TSP also must be investigated. For example, it is possible that skin lipids or dirt on the skin present below the TSP layer would disrupt the TSP layer. It is unclear whether results obtained with prior cleansing can be extrapolated to conditions (i.e., the battlefield) where such prior cleansing is not feasible.

Under battlefield conditions, the M291 skin decontamination kit, not Cetaphil® cleanser and water, would be used to decontaminate skin after exposure to permeants. The M291 kit contains an applicator pad impregnated with ——————— decontaminant resin. The resin is rubbed onto the contaminated surface. The powder is subsequently removed with soap and water when operational conditions permit. It is unclear whether results obtained following decontamination with Cetaphil® and water can be extrapolated to circumstances in which the M291 skin decontamination kit is used.

Independent Rescoring of Rhus Sensitization Sites
One potential source of bias in this study was that investigators were not blinded regarding which test sites on the forearm were treated with TSP prior to application of the urushiol. To eliminate the possibility of this bias, two independent dermatologists (William Cunningham, M.D. and James G. Marks, Jr., M.D.) were recruited to perform rescoring of the photodocumented reactive sites. Photographs of each individual site were cropped and mounted on separate scoring sheets for the dermatologists to grade the reactions without bias of seeing a range of sites or knowing site treatment assignment. The photographs were randomly ordered, with each photograph showing only one site without revealing the treatment applied to the site of the location on the arm. The dermatologists graded skin reactivity on the following scale, based on a modified North American Contact Dermatitis Group Scale:

Score	Description
0.0	Negative Reaction
0.5	Macular Erythema, Minimal Reaction Only
1.0	Weak Nonvesicular Reaction, Erythema Infiltration and Possible Papules
1.5	Between Score 1.0 and 2.0
2.0	Strong (Edematous or Vesicular Reaction)
2.5	Between 2.0 and 3.0
3.0	Spreading Bullous Ulcerative Reaction
3.5	Between Score 3.0 and 4.0
4.0	Extreme Spreading, Bullous Ulcerative Reaction

Evaluability criteria
The data sets analyzed by the sponsor consisted of the results from the 48 evaluable subjects who had progressed to Stage II and who had reactivity at unprotected sites at 96 hours post TSP/Rhus application.

Endpoints defined
Because the risk of bias was circumvented with the rescoring of the photographed sites by independent dermatologists, these were the scores used by Agency to evaluate efficacy. The efficacy variable was the difference in the Stage II dermatitis scores between the Rhus exposed TSP-protected and the Rhus exposed TSP-unprotected sites.

Statistical considerations:

A paired t-test and analysis of variance were used in this analysis to test whether TSP reduces skin reactivity to Rhus antigen. Two efficacy analyses were performed, one for each dermatologist's set of scores. The agreement between the sets of re-scored data from the two dermatologists, as well as their agreement with the scoring data from the original Principal Investigator, were assessed.

Because both high and low Rhus concentrations were tested, and because evaluations were performed by two dermatologists, four possible efficacy endpoints exist. A Bonferroni adjustment for multiple endpoints is a conservative approach under these circumstances to avoid inflating the risk of Type I error.

Study Results
Demographics

Demographics of 48 Evaluable Study Subjects		
Age	Mean	30.8 years
	Std. Dev.	5.9
	Median	31.0
	Range	(18,44)
Gender	Male	34 (70.8%)
	Female	14 (29.2%)
Race	Caucasian	44 (91.7%)
	Caucasian/Hispanic	2 (4.2%)
	African-American	1 (2.1%)
	Mixed	1 (2.1%)
From: Vol. 2.37, pg. 010		

Efficacy
Primary Efficacy Results
The following tables depict the distribution of skin reactivity scores recorded by the principal investigator and the two blinded scorers, based on the reaction induced by urushiol at the test sites at the clinical endpoint (96 hours). The first 4 tables depict the scores induced by the four different lots of urushiol, with the final table showing the overall distribution of scores from all 4 lots. These data are abstracted from Vol. 2.26, pp. 100-107 of the NDA submission. Scorer 1 was William Cunningham, M.D., and Scorer 2 was James G. Marks, Jr., M.D..

	Distribution of Skin Reactivity Scores					
	TSP Protected Sites			TSP Unprotected Sites		
	P.I.	Scorer #1	Scorer #2	P.I.	Scorer #1	Scorer #2
Lot No. 1, High Dose Challenge						
0	3	3	4		2	2
0.5	2	5	5		4	6
1.0	11	10	7		7	
1.5			2		3	2
2.0	2			8	1	5
2.5					1	1
3.0				10		
3.5						2
	TSP Protected Sites			TSP Unprotected Sites		
	P.I.	Scorer #1	Scorer #2	P.I.	Scorer #1	Scorer #2
Lot No. 1, Low Dose Challenge						
0	8	6	6		3	4
0.5	2	5	8		8	5
1.0	7	5	2	4	3	5
1.5		2	1		1	1
2.0	1			9	2	1
2.5			1		1	1
3.0				4		1
3.5				1		

	Distribution of Test Sites with Various Skin Reactivity Scores					
	TSP Protected Sites			TSP Unprotected Sites		
	P.I.	Scorer #1	Scorer #2	P.I.	Scorer #1	Scorer #2
Lot No. 2, High Dose Challenge						
0	1	2	1		2	2
0.5	4	2	4		1	1
1.0		2	1	1	3	1
1.5						2
2.0	1			1		
2.5						
3.0				4		
3.5						
	TSP Protected Sites			TSP Unprotected Sites		
	P.I.	Scorer #1	Scorer #2	P.I.	Scorer #1	Scorer #2
Lot No. 2, Low Dose Challenge						
0	2	2	2		1	1
0.5	3	4	3	2	4	4
1.0	1		1	1	1	1
1.5						
2.0				2		
2.5						
3.0				1		
3.5						

	Distribution of Test Sites with Various Skin Reactivity Scores					
	TSP Protected Sites			TSP Unprotected Sites		
	P.I.	Scorer #1	Scorer #2	P.I.	Scorer #1	Scorer #2
Lot No. 3, High Dose Challenge						
0	12	18	20		1	
0.5	6	4		1	9	8
1.0	3		2	2	7	4
1.5					3	5
2.0	1			8	2	4
2.5						
3.0				11		1
3.5						
	TSP Protected Sites			TSP Unprotected Sites		
	P.I.	Scorer #1	Scorer #2	P.I.	Scorer #1	Scorer #2
Lot No. 3, Low Dose Challenge						
0	14	15	13		1	
0.5	5	5	7		10	9
1.0	3	2		2	6	5
1.5			1		3	5
2.0				10	2	1
2.5			1			1
3.0				10		1
3.5						

	Distribution of Test Sites with Various Skin Reactivity Scores					
	TSP Protected Sites			TSP Unprotected Sites		
	P.I.	Scorer #1	Scorer #2	P.I.	Scorer #1	Scorer #2
Lot No. 4, High Dose Challenge						
0	28	37	33			
0.5	18	9	10		17	7
1.0	3	2	5	1	19	18
1.5		1			6	13
2.0	1	1	1	21	6	5
2.5				4	2	3
3.0			1	18		2
3.5				5		2
4.0				1		
	TSP Protected Sites			TSP Unprotected Sites		
	P.I.	Scorer #1	Scorer #2	P.I.	Scorer #1	Scorer #2
Lot No. 4, Low Dose Challenge						
0	32	41	38		1	2
0.5	12	7	9		17	9
1.0	5	2	2	5	17	15
1.5			1		9	13
2.0				23	6	5
2.5				1		2
3.0				14		3
3.5				7		1

	Distribution of Test Sites with Various Skin Reactivity Scores					
	TSP Protected Sites			TSP Unprotected Sites		
	P.I.	Scorer #1	Scorer #2	P.I.	Scorer #1	Scorer #2
High Dose Challenge						
0	44	60	58		5	4
0.5	30	20	19	1	31	22
1.0	17	14	15	4	36	
1.5		1	2		12	22
2.0	5	1	1	38	9	14
2.5				4	3	4
3.0			1	43		3
3.5				5		4
4.0				1		
	TSP Protected Sites			TSP Unprotected Sites		
	P.I.	Scorer #1	Scorer #2	P.I.	Scorer #1	Scorer #2
Low Dose Challenge						
0	56	64	59		6	7
0.5	22	21	27	2	39	27
1.0	16	9	5	12	27	26
1.5		2	3		13	19
2.0	1			44	10	7
2.5			2	1	1	4
3.0				29		5
3.5				8		1

For all four lots and for all three scorers, the distribution of scores at the TSP protected sites are shifted to the lower values, relative to the scores of the TSP unprotected sites. A comparison which adjusts for interindividual variances is the difference in dermatitis scores between TSP-treated and TSP-untreated sites challenged with the same urushiol dose within each subject , as assessed by the two independent blinded dermatologists. The null hypothesis, that TSP has no effect upon preventing development of Rhus dermatitis, predicts a difference of zero. To the extent that TSP protects against Rhus dermatitis, TSP-treated scores are lower than TSP-untreated scores, giving the difference in scores a negative value.

Difference in dermatitis scores between TSP-treated and TSP-untreated sites				
	High Dose (Rhus 1)		Low Dose (Rhus 2)	
	Scorer 1	Scorer 2	Scorer 1	Scorer 2
Mean difference	-0.7	-1.0	-0.7	-0.9
Standard error of measurement	0.07	0.09	0.07	0.10
t-statistic	-9.9	-10.4	-9.5	-8.9
P-value	<0.001	<0.001	<0.001	<0.001

The difference in dermatitis scores was significant, even after making a Bonferroni adjustment for multiple comparisons.

Sponsor calculated the Pearson correlation between the Principal Investigator, Scorer 1 and Scorer 2. As expected, the readings of the degree of inflammation were highly correlated. The correlations between Scorer 1 and 2 (0.88 for the low dose group, 0.79 for the high dose group) were greater than the correlation between the Principal Investigator and either of the Scorers (ranging from ——— The principal

investigator's scoring was based on examination in vivo, where cues from edema and microvesiculation are more easily detected than they can be from examination of photographs.

Safety

Extent of Exposure

Eighty one subjects were exposed to TSP and urushiol during Stage I of the study. Fifty of these subjects were exposed to TSP and urushiol twice (Stage I and Stage II).

Discontinuations

Only three subjects were removed from the study. Two screened subjects did not present to clinic for Stage I. One subject who underwent Stage I was unable to complete Stage II because of a change in work schedule. No subjects were discontinued from the study due to laboratory abnormalities.

Adverse Events

No adverse events were noted during this study. One subject (#31) died from multiple severe injuries in a motor vehicle accident five weeks after his participation in the study. Alcohol and excessive speed were determined to have contributed to the accident. The principal investigator felt that the subject's participation in the study was not a factor in his death.

Reviewer's Comments/Conclusions

This study's design was somewhat flawed in that the urushiol was applied differently to TSP-treated and TSP-untreated sites. This difference created an experimental bias of uncertain direction in the study, but it seems unlikely that the relatively small difference in the way in which urushiol was applied to the skin could account for the marked difference in skin reactivity between TSP-treated and untreated sites.

This study demonstrated that pretreatment with TSP reduces the severity or blocks the clinical manifestation of rhus-mediated dermatitis. No treatment-emergent adverse events were associated with TSP use.

Because of the way in which this study was designed and conducted, it does not resolve the following issues concerning TSP efficacy:

- It is unclear whether pre-treating the skin sites with 70% isopropyl alcohol prior to TSP application is necessary for TSP to block urushiol reactivity.
- It is unclear whether TSP needs to "set" 30 to 60 minutes after application before it creates an effective barrier to urushiol penetration.
- It is unclear whether TSP would be as effective a barrier when applied by soldiers, using their fingertips to spread the TSP, as it appears to be when applied by medical technicians, using a steel spatula to spread the TSP.
- It is unclear whether TSP is as effective if urushiol or another permeant were to be left in place on test sites for longer than 4 hours.