CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-084

STATISTICAL REVIEW(S)

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STATISTICAL/CLINICAL REVIEW AND EVALUATION

NDA#:	NDA 21,084
Applicant:	US Army Medical and Materiel Command
Name of Drug:	Topical Skin Protector (TSP)
Documents Reviewed:	Volumes 1, 31-41, dated August 19, 1999
Type of Report:	NDA review
Indication:	Protection of skin from contact with chemical warfare agents (CWA)
Medical officer:	Martin Okun, M.D. (HFD-540)

Introduction

The sponsor submitted reports of two controlled clinical trials, "An Assessment of the Ability of the Topical Skin Protector (TSP) to Protect Against Contact Dermatitis to Rhus Antigen" (Poison Ivy Study) and "The Protective Efficacy of the Topical Skin Protectant (TSP) Against Methyl Nicotinate under Sweating Conditions" (Sweat Study). The objective of these studies is to demonstrate safety and efficacy of topical skin protector (TSP) in protection of skin from contact with chemical warfare agents (CWA).

I. POISON IVY STUDY

Design: The objective of this study was to assess the ability of TSP to protect subjects against contact with poison ivy. In this study, poison ivy resin (urishiol) is used as a surrogate in place of sulphur mustard and other CWA.

This was an open bilateral trial. Each subject served as his or her own control. In Stage I, the minimal threshold concentration (MTC) for each subject was determined. In Stage II, each subject had 4 pairs of test sites (two pairs on each forearm). Each pair of sites consisted of one TSP protected (TSP+) and one TSP unprotected (TSP-) site. Two concentrations were used: rhus1=MTC on one pair of sites and rhus2 on the other pair of sites. After 96 hours of urishiol application, the skin sites were evaluated by a Principal Investigator (PI). The photographs of the skin sites arms were taken. The PI graded the sites using a modification of the North American Contact Dermatitis Group (NACDG) scoring system. This is a 9-point scale ranging from 0.0 to 4.0:

0.0 = Negative reaction
0.5 = Macula erythema, minimal reaction only
1.0 = Weak nonvesicular reaction, erythema, infiltration and possible papules
1.5 = between 1.0 and 2.0
2.0 = Strong (edematous or vesicular reaction)
2.5 = Between2.0 and 3.0
2.0 = Spreading, bullous ulcerative reaction
3.5 = between 3.0 and 4.0
4.0 m= Extreme spreading, bullous ulcerative reaction

The sites were designated as:

Site	Side	Location	TSP Protected	Urushiol Concentration
TSP-rhus 1 right	Right	Forearm	N	higher (rhus 1)
TSP-rhus 1 left	Left	Forearm	N	higher (rhus 1)
TSP+rhus 1 right	Right	Forearm	Y	higher (rhus 1)
TSP+rhus 1 left	Left	Forearm	Y	higher (rhus 1)
TSP-rhus 2 right	Right	Forearm	N	lower (rhus 2)
TSP-rhus 2 left	Left	Forearm	N	lower (rhus 2)
TSP+rhus 2 right	Right	Forearm	Y	lower (rhus 2)
TSP+rhus 2 left	Left	Forearm	Y	lower (rhus 2)

higher= Minimum Threshold Concentration (MTC) of rhus antigen for a particular subject as determined by Stage I (rhus 1)

lower= The next weaker dilution of below the MTC for a particular subject as determined by Stage I (rhus 2)

Re-scoring study: Because the PI evaluation was not blinded and was potentially biased, the FDA requested the sponsor to perform a blinded analysis of the photographs. Photographs documenting the results of the various TSP–treated and TSP–untreated skin sites were re-scored and the resulting scores statistically re-analyzed based on the new data. Two independent dermatologists (scorers) performed the re-scoring of the photographs. Scorers were oriented to the scoring procedure and the modified NACDG scoring system. A random number generator was used to sort the photographs for re-scoring. The re-scoring was performed as follows:

A duplicate set of photographs was developed from the original study negatives. These photographs were prepared in the following manner: Photographs of each individual treatment site were cropped and mounted on separate scoring sheets (one per reaction site) for the dermatologists to grade the reactions without bias of seeing a range of sites. There were eight photographs to score per subject (384 total). A random number was assigned to the test site depicted on each photo. These numbers were entered into a secured list. The subjects were identified only by their number from the original study; no individual's name was used in the re-scoring study. The blinded list was secured in a sealed envelope until all re-scoring was completed.

Each photograph, associated with the assigned random number only, was mounted on a 8½ x 11 inch sheet of paper, which also contained a textual description of the modified NACDG scale. Because of the cost of preparing an additional set of photo-documents from the negatives, the same set of photo-documents was used independently by each scorer for the scoring of the reaction sites. A separate set of accompanying forms for each reaction site was provided to each scorer for recording his actual scores.

Primary efficacy variable: the difference in the dermatitis scores by the blinded scorer between the TSP protected and TSP unprotected sites. The set of blinded, randomized scores was also compared against the previous unblinded scoring performed by the original Principal Investigator (PI), providing a secondary efficacy variable.

Statistical Methods: The primary statistical methods in the re-analysis was a paired t-test. The paired t-test was performed separately for each independent scorer, on the mean difference of the paired TSP+ and TSP- site scores, averaged across left and right arms. A separate paired t-test was performed for each low and high rhus dose level resulting in two t-tests for each scorer.

Although the dermatitis scale is a 9-point categorical scale, averaging across the arms makes the scale less discrete. The assumptions of normality and equal variances were evaluated.

In addition, the Pearson correlation coefficients were calculated to evaluate the correlation between the two scorers, between each scorer and the PI, and between the average scorers and the PI.

There was only one primary efficacy variable for the Poison Ivy Study, the difference in the dermatitis scores between the TSP–protected and TSP–unprotected sites. Two efficacy analyses for the primary endpoint of the study were performed, one for each of the scorers. The agreement between the sets of re-scored data from the two scorers was assessed, as well as, the agreement between each of the two dermatologists and the original Principal Investigator's scores.

Multiple comparisons adjustment: ***Two doses and two scorers were used in this study. In order to protect the Type I error at the 0.05 level, this reviewer applied a p-value adjustment for multiple comparisons using a Bonferroni adjustment procedure. This means that in this study, all efficacy comparisons were made at the 0.05/4=0.0125 significance level.***

Results of the Stage II of the Poison Ivy Study:

Demographics:

Number of subjects enrolled: Fifty men and women were enrolled. Race and Gender of all 50 subjects was as follows: Of the fifty subjects, 34 were male, 16 were female. One subject was African-American, one was a female of "mixed" race, 3 were Caucasian/Hispanic and 45 were Caucasian.

Inevaluable subjects: 2, evaluable subjects: 48.Two subjects had negative skin reactions at all test sites at 96 hours. One did not react at all in Stage II despite being reactive in the preliminary Stage I (subject #16). The other subject had a consistently delayed reaction to rhus antigen in both Stage I and II (subject #86). Her reactions were ultimately positive and were assessed at 168 hours. As a result, these two subjects were considered to be inevaluable and were excluded from the demographics and data below and data set analysis since they did not react during the 96 hour limit set in the protocol. Subject #16 was a 21 year old Caucasian/Hispanic female and subject #86 was a 43 year old Caucasian female.

Race, Gender and Age: There were 34 men (71%) and 14 women (29%) ranging in age from 18-44 years with a mean age of 30.8 years. Forty four (92%) were Caucasian or Caucasian/Hispanic, one female was African American, and one female was of "mixed" race.

Measurement of Treatment Compliance: The application and removal of all test materials was performed only by the investigator and/or study technicians. The investigator or study technicians ensured that the subjects were contacted to remind them of follow up dates and times. All subjects who actually had test materials applied for Stage I or II did return on time for removal of test materials. All subjects returned for the 96-hour evaluation. All ten sites were evaluated on each volunteer.

Efficacy:

The primary analysis used the scores averaged over the two arms. Unlike the PI, the blinded scorers had instances where the TSP- sites were given lower score than TSP+ sites. The mean differences for scorers were lower than for the PI. The summary statistics for the differences of TSP+ and TSP- sites averaged over left and right arms are shown in Table 1. The histograms of the distributions of the differences were roughly bell-shaped which justified the use of the t-test. The paired t-test presented in Table 1 found that the mean differences for each scorer and the PI had unadjusted $p<0.001$. Therefore, there was a statistically significant difference between TSP+ and TSP- at the adjusted 0.0125 significance level.

Table 1. Difference in dermatitis scores between TSP-treated and TSP-untreated sites. Poison Ivy Study

	High Dose (Rhus 1)			Low Dose (Rhus 2)		
	Scorer 1	Scorer 2	PI	Scorer 1	Scorer 2	PI
N	48	48	48	48	48	48
Mean	-0.7	-1.0	-2.1	-0.7	-0.9	-2.0
STD	0.48	0.66	0.66	0.51	0.67	0.59
Standard error	0.07	0.09	0.10	0.07	0.10	0.08
t-statistic (paired t-test)	-9.9	-10.4	-21.6	-9.5	-8.9	-23.3
Unadjusted p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

For the differences between TSP+ and TSP- site score, Table 2 provides the correlation between each of the scoring for each dose level. All correlations were statistically

significant with higher correlations for the low dose than for high dose. The highest correlations were between the two scorers: 0.88 for the low dose and 0.79 for the high dose.

Table 2. Correlation between the scorers and PI by dose level. Poison Ivy Study		
(TSP+) minus (TSP-)	Correlation	p-value
Low Dose		
PI vs. Scorer 1	0.69	<0.001
PI vs. Scorer 2	0.67	<0.001
Scorer 1 vs. Scorer 2	0.88	<0.001
High Dose		
PI vs. Scorer 1	0.43	0.002
PI vs. Scorer 2	0.34	0.016
Scorer 1 vs. Scorer 2	0.79	<0.001

Efficacy Subgroup Analysis

An efficacy subgroup analysis was performed in the following subgroups: males, females, under 30 years, and 30 years or older. This analysis showed that there was a statistically significant difference between TSP+ and TSP- in favor of TSP-treated sites with $p<0.002$. The results indicate that the magnitude of the TSP effect may depend on the age of the subject.

Safety Evaluation

Extent of Exposure: In each of those volunteers the exposure totaled only 0.5 grams apiece (0.1 gram per each of four test sites and one control site). The exposure was limited to 4 hours (from application to wash off).

Adverse Events: There were no adverse events attributable to the TSP. In no instance was there any irritation observed at the TSP "Control" sites. Six (12.5%) TSP-protected sites had a strong edematous or vesicular reaction compared with 13 (27.1%) TSP unprotected sites ($p=0.73$).

Deaths: Subject #31 died within a few weeks after completion of the protocol due to a motor vehicle accident unrelated to his participation.

Clinical Laboratory Evaluation: The only laboratory studies involved in this protocol were serum tests for HIV and pregnancy (females only).

Reviewer's Conclusions on the Poison Ivy Study:

The efficacy analysis of the Poison Ivy Study supports the claim that TSP protected sites have statistically significantly smaller dermatitis score than TSP-unprotected sites 96 hours after rhus antigen application ($p<0.001$).

An efficacy subgroup analysis was performed in the following subgroups: males, females, under 30 years, and 30 years or older. This analysis shows that there was a statistically significant difference between TSP+ and TSP- in favor of TSP-treated sites with $p<0.002$. The results indicate that the magnitude of the TSP effect may depend on the age of the subject.

II. SWEAT STUDY

The objective of this study was to test the effectiveness of TSP under sweating conditions, namely, to evaluate whether sweat droplets produced under the TSP layer can compromise the TSP barrier qualities.

In this study, methyl nicotinate (Mnic), was chosen as the challenge agent because the non-immunologic contact reaction (NICR) that it produces upon contact with the skin results in vasodilatation causing erythema. Erythema can be assessed by visual scoring and by measurements made by instruments such as the laser Doppler imager. Laser Doppler velocimetry (LDV) evaluates blood flow within the cutaneous microcirculation, and can detect changes in blood flow due to vasodilatation via flux measurements.

Study Procedures: Three pairs of test sites were identified on the volar surface of both forearms of subjects. TSP was evenly applied at each of three sites of one forearm chosen at random to provide a 0.1 mm layer of TSP at each site. The corresponding sites on the contra lateral forearm remained TSP-untreated. Site pairs were then defined as two sites, one on each arm, with the same relative location. Both sites within a given site pair always received the same of three possible challenges: 2.5 mM Mnic challenge, vehicle challenge, or no challenge. At random, either the proximal (elbow) or distal (wrist) site pairs were chosen for each subject to receive Mnic challenge. The remaining sites then were randomly assigned to either the vehicle challenge or no challenge. One hour after TSP application, subjects entered a "hot room" at 100°F, for a preconditioning period of 80 minutes, to induce sweating. Site pairs were challenged per the randomization schedule for a two minute time period. Visual scores of erythema were provided at two minute intervals. Flux measurements derived from Laser Doppler (LDV) scans were performed at baseline and approximately 13 minutes post-challenge. TSP was removed 22 minutes after challenge.

Study Design

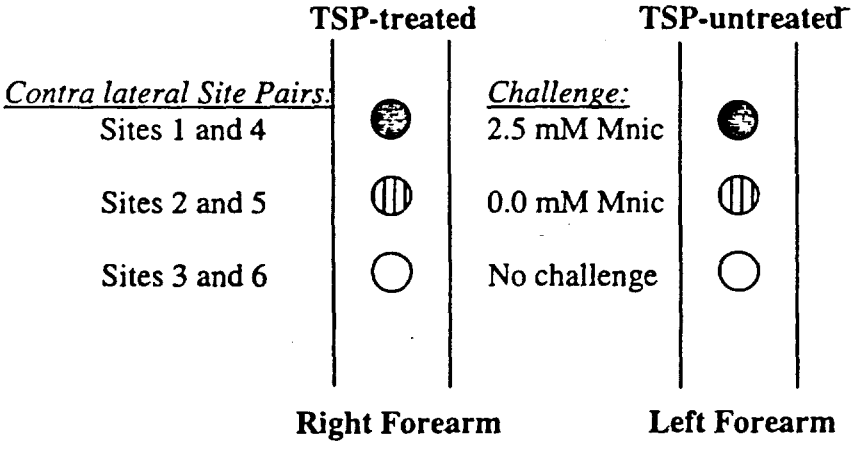
This was an open label, bilateral, randomized, complete block design study. Visual assessment of erythema and scanning laser Doppler imaging were used to compare the efficacy of the TSP protective barrier compared to the numerical values obtained without TSP under sweating conditions.

The ability of TSP to protect against Mnic challenge was evaluated relative to no treatment (unprotected skin designated as TSP-untreated). For both the TSP-treated and TSP-untreated sites, the 2.5 mM Mnic-challenge, the vehicle challenge (0.0 mM Mnic), and 'no

challenge' were performed. A summary of all treatment/challenge regimens are listed below:

Treatment ASSIGNMENT	CHALLENGE AGENT ASSIGNMENT
TSP	2.5 mM Mnic
TSP	Vehicle control
TSP	No challenge
Unprotected Skin	2.5 mM Mnic
Unprotected Skin	Vehicle control
Unprotected Skin	No challenge

Test article assignment was randomized across right and left arms. Each of the three sites on one arm was paired with contra lateral sites on the other arm, forming three 'contra lateral site pairs'. Each of these site pairs had one site that received treatment with TSP and one site that remained untreated. The 2.5 mM Mnic challenge was randomized across the distal (wrist) or proximal (elbow) sites to provide maximum variation in the range of perspiration encountered. Randomization of the vehicle or the 'no challenge' designation was performed across all three site pairs. An example of this randomization and the contra lateral site pairs is shown below:



Comparison between the intensity of visible erythema and change in cutaneous microcirculation for the site receiving TSP with Mnic challenge against the site with unprotected skin with Mnic challenge provided the ability to determine the relative efficacy of TSP to protect against Mnic-induced NICRs under sweating conditions.

TSP was applied to all three sites designated for application on either the right or left forearm in accordance with the randomization schedule. The other three sites on the contra lateral forearm remained untreated and unprotected and served as the control-Mnic challenge (application and removal)

Since the objective of this investigation was to evaluate the effect of active sweating on the barrier efficacy of the TSP, the TSP was applied prior to onset of sweating and perspiration. A "wear time" of 60 minutes was chosen after TSP application prior to hot room entry and challenge in order to be consistent with previous clinical and non-human

pharmacological testing previously performed. Thus, subjects were required to remain in the ambient conditioning room for 60 minutes after TSP application.

Three sites on one forearm received the TSP application and three contra lateral sites received no treatment and served as the controls. Site pairs were defined as two sites, one on each arm, with the same relative locations. Both sites within a given site pair always received the same challenge.

Mnic challenge was performed after the following steps: application of TSP, a 60 minute waiting period, 80 minutes of thermal stress in the heating room and verification of active sweating and perspiration.

One contra lateral site pair received challenge with a 2.5 mM of Mnic. One contra lateral site pair received challenge with vehicle. One contra lateral site pair received no challenge and served as the unchallenged control.

Blinding and efficacy variables

The **primary efficacy measurement**, LDV, was instrumental evaluations and free of investigator bias. On the other hand, the visual assessment of erythema was unblinded and potentially biased because the presence of the TSP test article was clearly visible on the subject's forearm. This reviewer used visual assessment as the **secondary efficacy** variable. The photographs were taken but not evaluated in this study.

Visual Scores:

Visual evaluation of erythema was performed by a trained evaluator on all test sites. The unblinded visual scores were used to corroborate the LDV data. Evaluators used a seven-point scale in which integer scores are defined below. Half-integer scores were permitted when appropriate in the opinion of the evaluator.

0 = No reaction
1 = Mild reaction; minimal macular erythema faint but definitely pink usually covering the entire test site
2 = Moderate reaction; moderate macular erythema, definite redness, possible edema.
3 = Strong to severe reaction; intense redness, probable edema, possible spreading

Statistical analysis

The statistical analyses were designed to determine if the TSP protected the skin against the penetration of Mnic under sweating conditions. The test sites were three sites each on the right and left forearms of the subjects for a total of six sites arranged as three contra lateral site pairs. Treatment with the TSP was randomly assigned to either all sites on the right arm or all sites on the left arm such that for each contra lateral site pair, one site

received treatment with TSP (TSP-Treated) and one site was designated as TSP-Untreated. Three types of challenge (0.0 mM Mnic, 2.5 mM Mnic and "No Challenge") were performed to both sites of the pre-randomized contra lateral site pairs (one site on each forearm).

The primary efficacy variable was Laser Doppler Velocimetry (LDV) blood flow (flux) measurements taken before removal of the TSP (at approximately T13).
The following analyses were performed:

- TSP-treated *versus* TSP-untreated by Type of Challenge, using the paired t-test
- Comparison of Types of Challenge (0.0 mM Mnic *versus* 2.5 mM Mnic *versus* "No Challenge") by TSP application (TSP-treated and TSP-untreated) using the Friedman rank test.

The secondary efficacy variable was the visual assessment of erythema. The visual score was taken at baseline, one hour after the application of the TSP, immediately after the Mnic irritant was applied (T0), at 2 (T2), 4 (T4), 6 (T6), 8 (T8), and 10 (T10) minutes after the application of the Mnic irritant, upon removal of the TSP (approximately T22) and after the post-wash procedure (approximately T27). The evaluation of the secondary efficacy variable was potentially biased due to lack of blinding.

Between-treatment analyses were conducted for the visual scores at each time point using analysis of variance at each of the post-treatment time points. Baseline data were to be used as covariates; however, all visual erythema baseline scores were zero. The following analyses were performed:

- TSP-treated *versus* TSP-untreated by Type of Challenge
- Comparison of Types of Challenge (0.0 mM Mnic *versus* 2.5 mM Mnic *versus* "No Challenge") by TSP application (TSP-treated or TSP-untreated).

Disposition of Subjects

42 subjects (10 male, 32 female) were enrolled, 37 subjects (10 male, 27 female) completed. Subjects were male and female, unrestricted as to race or ethnicity, between 18 – 55 years of age, and in good general health as established through a medical examination.

There was no difference between TSP-treated and TSP untreated at baseline (before challenge) relative to visual assessment (zero score in both groups) and LDV flux measurements ($p<0.05$).

Analysis of Efficacy

Silicone replicas showed that all subjects exhibited active perspiration under "hot room" conditions. Test sites that were not treated with TSP, but that were challenged with Mnic exhibited clear erythema from the NICR with an onset of 2 to 4 minutes. The erythema increased gradually in intensity through the visual evaluation at 10 minutes, and then appeared to decrease between 22 and 27 minutes post-challenge. Subjects who did not respond to the Mnic challenge solutions with a visible NICR on those sites not pretreated with TSP were not included in the sponsor's efficacy analyses. Clinical photographs were made of all test sites at approximately the same time that the final visual scores were rendered. These photographs were not evaluated in this study.

Reviewer's Comments:

1. ***In this review, Doppler flux measurement was the primary efficacy variable. Unblinded visual scores recorded at pre- and post-challenge timepoints were potentially biased and therefore, were used as a secondary efficacy variable to corroborate the primary LDV analysis.***

2. ***In the sponsor's report, of the 37 completed subjects, only 33 subjects were included in the analysis of the Doppler flux scores. Four subjects (# 17, #33, # 37, and #55) were excluded from the statistical analysis of the Doppler flux scores. The sponsor classified these four subjects as "Non-Responders", although these subjects were not excluded from the visual scores analysis. The sponsor claimed that these subjects did not respond to the challenge agent (Mnic) and therefore, their lack of a response to the Mnic challenge made it impossible to determine the degree of protection provided by the TSP.***

   This reviewer conducted two statistical analyses of the Doppler flux scores in the Sweat Study: one analysis for the 33 subjects and another analysis for all 37 completed subjects.

Results of the Sweat Study

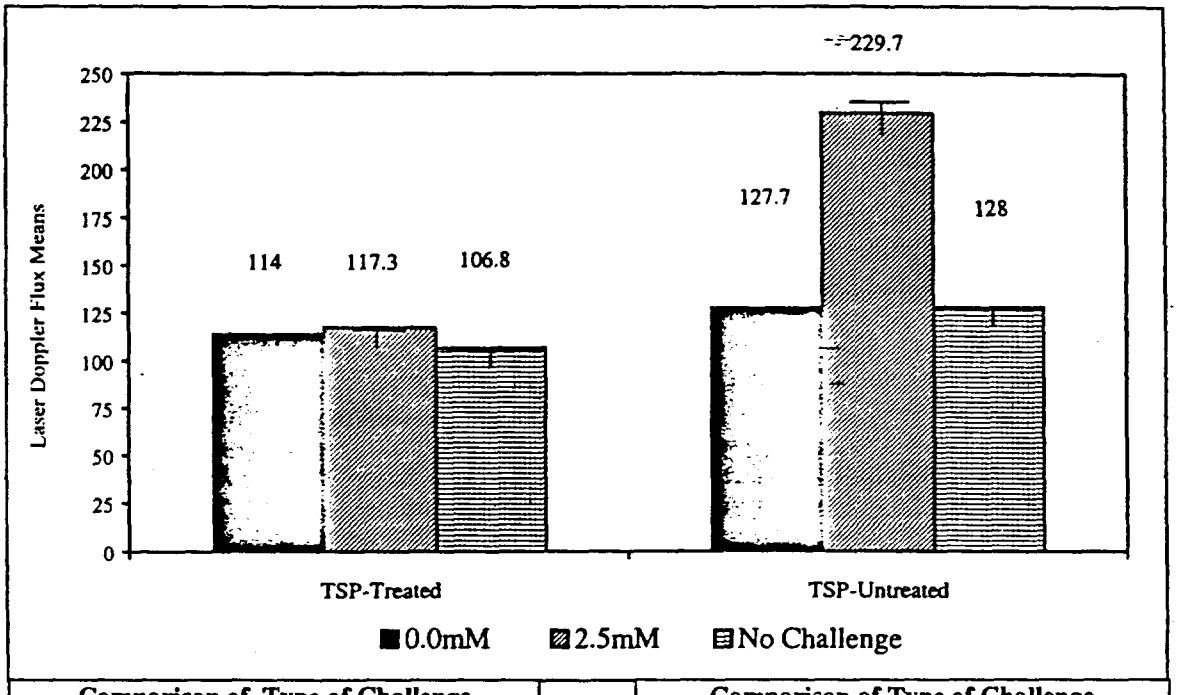
Results from the analysis of the Doppler flux data for the 33 subjects are shown on Figure 1. This figure displays averages of flux measurements by LDV recorded from the test sites that were treated in the same way for all subjects. These data are also presented in table format below the figure along with mean ranks for each pretreatment and challenge condition. Two groups of data are illustrated as histograms in the figure, one for TSP-treated and one for TSP-untreated sites. Each group contains laser Doppler flux means for sites that received a vehicle challenge, a 2.5 mM Mnic challenge, or no challenge. Flux data are presented in relative units normalized for instrument gain.

The **primary efficacy** comparison was comparison of TSP-treated versus TSP-untreated for those sites receiving a 2.5 Mnic challenge. The analysis of data for 33 subjects showed that the response to Mnic was reduced by 112.5 (49%) due to pretreatment with TSP. This decrease is statistically significant at the $p<0.0001$ level. Flux values recorded for TSP-treated sites were

lower than TSP-untreated sites in every pair of sites. The analysis of data for all 37 subjects showed that the response to Mnic was reduced by 101.2 (44%) due to pretreatment with TSP. This decrease is statistically significant at the p<0.0001 level.

FIGURE 1: LASER DOPPLER ANALYSIS

Analysis of Scanning Laser Doppler Velocimetry Data for TSP-Treated and for TSP-Untreated Sites (N=33)



Comparison of Type of Challenge For TSP-Treated Sites		
Type of Challenge	**Mean Rank**	**Mean Flux (± SEM)**
0.0mM Mnic	2.09	114.01 ± 7.51
2.5mM Mnic	2.12	117.26 ± 5.99
No Challenge	1.79	106.82 ± 6.03
P-value	0.33	---

Comparison of Type of Challenge for TSP-Untreated Sites		
Type of Challenge	**Mean Rank**	**Mean Flux (± SEM)**
0.0mM Mnic	1.55	127.68 ± 6.66
2.5mM Mnic	3.00	229.72 ± 15.20
No Challenge	1.45	128.01 ± 6.60
P-value	0.0001*	---

Additional analyses were conducted to evaluate the effect of the different types of challenge by treatment. The "TSP-untreated" sites that received a 2.5 mM Mnic challenge had significantly ($p < 0.0001$) higher flux values than either the vehicle challenged or unchallenged sites. The sites that were pretreated with TSP are not significantly different from one another ($p=0.33$). The averages of flux measurements from vehicle, 2.5 mM MNIC or no challenge are nearly the same for sites protected with TSP.

Subgroup Analysis (by agegroup and gender) for the Doppler flux data

There was a statistically significant difference ($P<0.001$) between the TSP-treated and TSP-untreated in both age subgroups (subjects <= 40 years and above 40 years).

There was a statistically significant difference (P<0.001) between the TSP-treated and TSP-untreated in both male and female subgroups.

Of the 37 completed subjects, 34 (92%) Caucasians. Efficacy subgroup analysis by race was not performed because there were only 2 Asians and one black subject.

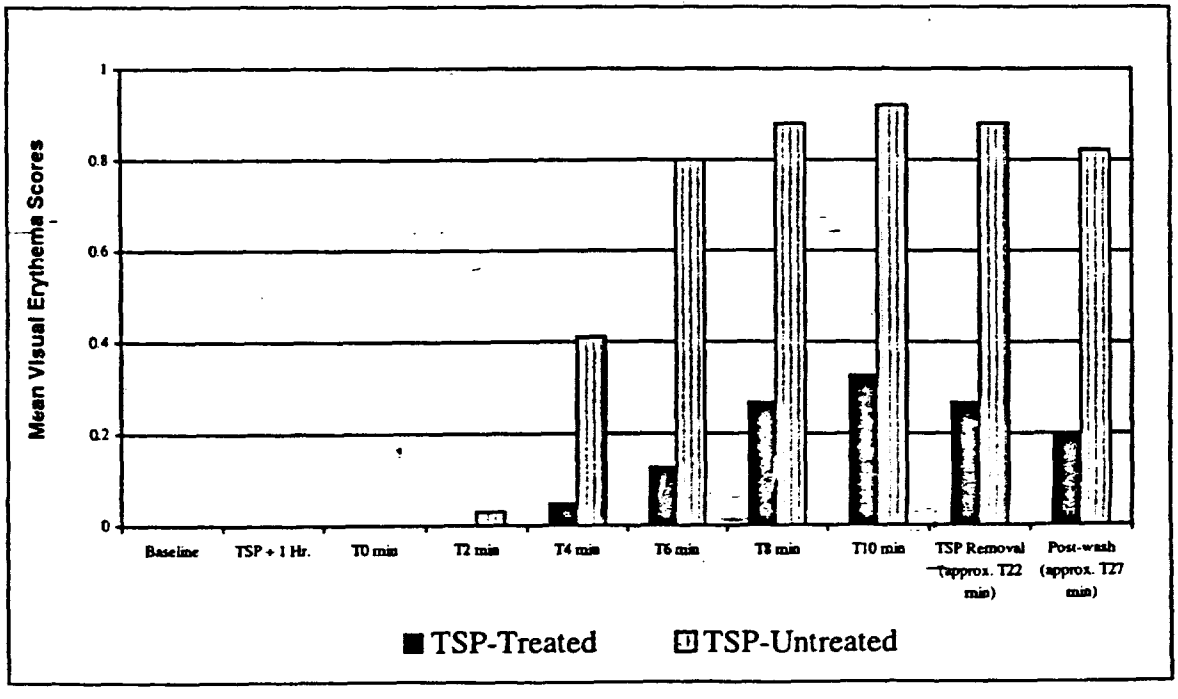
Visual scores Analysis.

Visual scores were obtained in unblinded fashion and therefore were not free of the Investigator bias. The secondary efficacy analysis of the visual scores is summarized in the histograms and tables presented in Figures 2, 3, and 4. Visual scoring employed a modified Draize method for erythema on a scale from 0 to 3 with half-integer values. Post-challenge times are indicated by Tt where t is the post-challenge time from 2 minutes to 10 minutes (Example: T2 = 2-minutes post-challenge). Data pairs labeled as "TSP Removal" and "Post-Wash" are average scores observed at the times that these procedures were conducted during the protocol.

a) TSP-treated vs. TSP-untreated

Figure 2 presents data for Mnic challenged sites for TSP-treated and TSP-untreated groups together. Average values of visual scores for all Mnic challenged sites are presented as pairs of histograms showing TSP-treated versus TSP-untreated groups at different post-challenge times. For all histogram pairs, TSP-treated sites are shown on the left, while TSP-untreated site scores are on the right. After T2, average scores for the TSP-treated group are always significantly (p<0.0001) lower than the TSP-untreated group. Reductions in scores resulting from TSP-treatment range from 64% at T10 to 88% at T4.

FIGURE 2: VISUAL ERYTHEMA ANALYSIS
Analysis of Mean Visual Scores of TSP-Treated *versus* TSP-Untreated Sites Challenged with 2.5mM Mnic at Various Post-Challenge Times (33 subjects)



Mean Visual Scores for Challenge with 2.5-mM Mnic + STD					
Application Code	**Baseline**	**TSP + 1 Hr.**	**T0**	**T2**	**T4**
TSP-Treated	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.05 ± 0.20
TSP-Untreated	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.03 ± 0.17	0.41 ± 0.46
ANOVA p-value	ND	ND	ND	0.2301	0.0001*

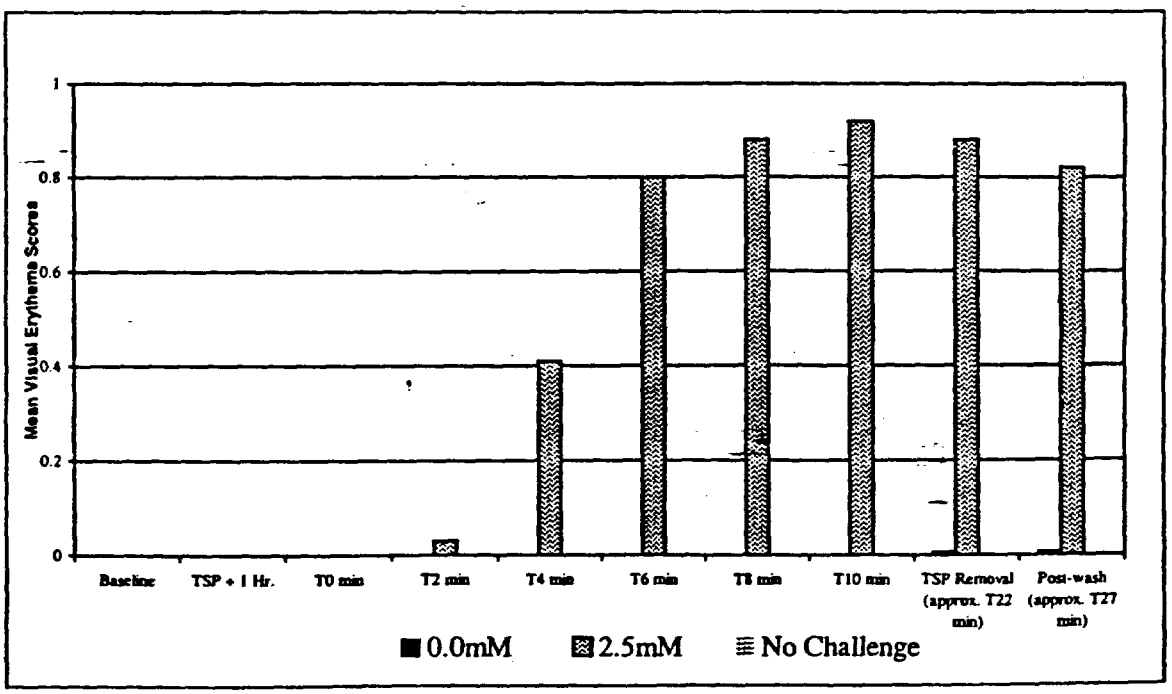
Application Code	**T6**	**T8**	**T10**	**TSP Removal (approx. T22)**	**Post Wash (approx. T27)**
TSP-Treated	0.13 ± 0.27	0.27 ± 0.37	0.33 ± 0.40	0.27 ± 0.36	0.20 ± 0.33
TSP-Untreated	0.80 ± 0.38	0.88 ± 0.27	0.92 ± 0.25	0.88 ± 0.30	0.82 ± 0.33
ANOVA p-value	0.0001*	0.0001*	0.0001*	0.0001*	0.0001*

b) Different types of challenge by treatment

Data presented in Figure 3 show the effect of three different types of challenge on the TSP-untreated sites. The table below the figure tabulates these data and presents the standard deviation for each mean. One can see from the table that for those sites that received no challenge, scores recorded for all subjects were zero. Similar to these data, visual scores for sites that were vehicle challenged were zero except observation times of T22 and T27 when the mean score was 0.01. This average reflects a score of 0.5 that was recorded for one of the responders with all other subjects receiving a score of zero. When displayed graphically, histograms from the vehicle challenged or unchallenged groups do not appear except for the near zero bars for vehicle challenged sites at T22 and T27. The average scores for TSP-untreated and 2.5 mM Mnic challenged sites are large. Mean scores increase from T2 and reach a maximum of 0.92 at T10. In the time elapsed from observations at T10 to T22, the average score shows a slight, but insignificant decrease. However, this trend continues at T27, suggesting that the mean scores for erythema reached its maximum between 10 and 22 minutes post-challenge. Scores for TSP-untreated Mnic challenged sites were always significantly higher than vehicle challenged and unchallenged sites after 4 minutes post-challenge.

FIGURE 3: VISUAL ERYTHEMA ANALYSIS

Analysis of Mean Visual Scores of Various Types of Challenge for TSP- Untreated Sites



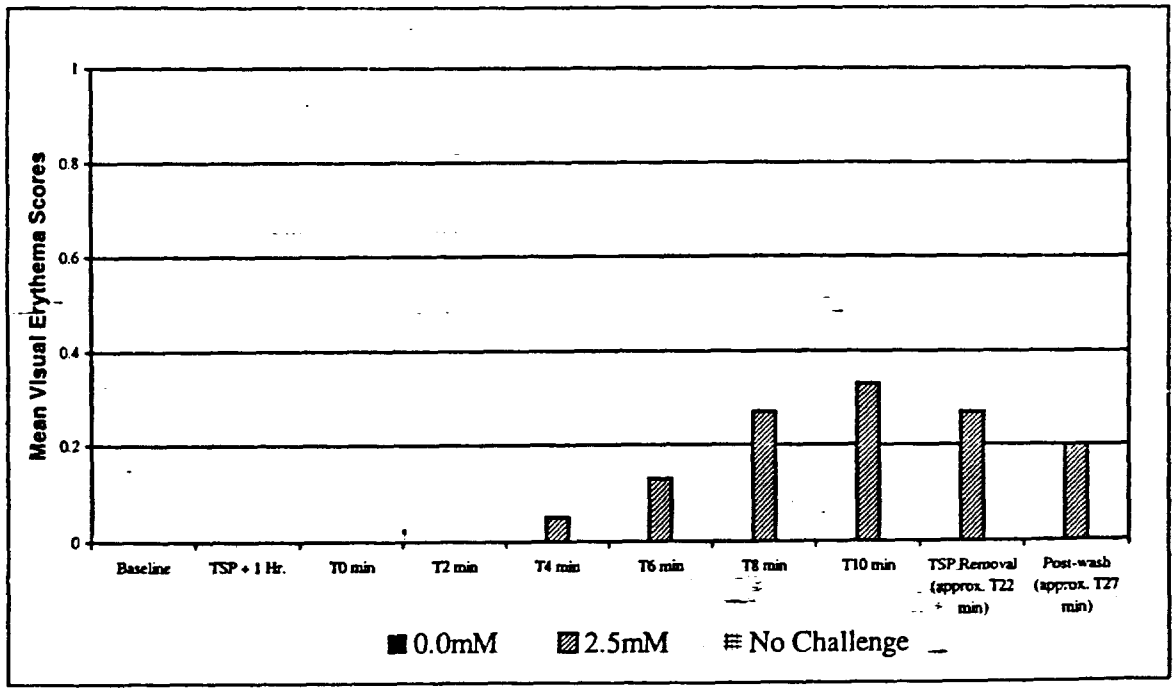
Mean Visual Scores for TSP-Untreated Sites ±STD					
Type of Challenge	**Baseline**	**TSP + 1 Hr.**	**T0**	**T2**	**T4**
0.0mM	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
2.5mM	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.03 ± 0.17	0.41 ± 0.46
No Challenge	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
ANOVA p-value	ND	ND	ND	0.2322	0.0001*

Type of Challenge	**T6**	**T8**	**T10**	**TSP Removal (approx. T22)**	**Post Wash (approx. T27)**
0.0mM	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.01	0.01
2.5mM	0.80 ± 0.38	0.88 ± 0.27	0.92 ± 0.25	0.88 ± 0.30	0.82 ± 0.33
No Challenge	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
ANOVA p-value	0.0001*	0.0001*	0.0001*	0.0001*	0.0001*

Data in Figure 4 present average scores for all challenge groups for TSP-treated sites. Data for challenge groups of 0.0 mM Mnic (vehicle challenge), 2.5 mM Mnic, and no challenge are presented in the table and the histogram at various post-challenge times. In Figure 4, values for vehicle challenged sites were zero for TSP-treated sites even at T22 and T27. Similar to Figure 3, data for vehicle challenged and unchallenged sites exhibit visual scores of zero for all subjects at all post-challenge times. The only bar graphs that appear in this graph are the nonzero data for sites that received 2.5 mM Mnic challenge. Average scores increase from zero at T2 to 0.33 at T10. These scores are significantly higher than the vehicle challenged and unchallenged sites from T6 through T27 minutes post-challenge.

FIGURE 4: VISUAL ERYTHEMA ANALYSIS

Analysis of Mean Visual Scores of Various Types of Challenge for TSP-Treated Sites



Mean Visual Scores for TSP-Treated Sites ± STD					
Type of Challenge	**Baseline**	**TSP + 1 Hr.**	**T0**	**T2**	**T4**
0.0mM Mnic	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
2.5mM Mnic	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.05 ± 0.20
No Challenge	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
ANOVA p-value	ND	ND	ND	ND	0.0677

Type of Challenge	**T6**	**T8**	**T10**	**TSP Removal (approx. T22)**	**Post Wash (approx. T27)**
0.0mM Mnic	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
2.5mM Mnic	0.13 ± 0.27	0.27 ± 0.37	0.33 ± 0.40	0.27 ± 0.36	0.20 ± 0.33
No Challenge	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
ANOVA p-value	0.0005*	0.0001*	0.0001*	0.0001*	0.0001*

Safety Evaluation

Each subject was exposed to TSP for a period of approximately 170 minutes during their participation in the study. There were no adverse events reported during the course of the study.

Additional information on the safety of TSP is provided in Table 3 which shows the average scores for the sites that were TSP-treated, but that received no challenge.

Table 3. Mean Visual Scores for Challenge with "No Challenge" ± STD					
Application Code	**Baseline**	**TSP + 1 Hr.**	**T0**	**T2**	**T4**
SP-Treated	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
TSP-Untreated	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
ANOVA p-value	ND	ND	ND	ND	ND

Application Code	**T6**	**T8**	**T10**	**TSP Removal (approx. T22)**	**Post Wash (approx. T27)**
TSP-Treated	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
TSP-Untreated	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
ANOVA p-value	ND	ND	ND	ND	ND

Table 3 shows that a score of zero was recorded for not challenged site on every subject at all time points. This data supports the claim that TSP is safe and nonirritating to the skin where it is applied. It was also observed that small droplets of sweat appeared on the surface of the TSP after subjects had entered and stayed in the "hot room" long enough to induce sweating. These droplets appeared as very small beads of sweat that remained spherical in shape throughout the "hot room" procedure.

Reviewer's Conclusions on the Sweat Study:

The primary efficacy analysis showed that there was a statistically significant difference in favor of TSP protection relative to the Doppler flux measurements ($p<0.001$).
The subgroup analysis showed that there was a statistically significant difference in favor of TSP protection relative to the Doppler flux measurements in both males and females ($p<0.001$) and in both subjects under 40 years old and above 40 years ($p<0.001$).

Secondary analysis of the unblinded visual scores supported the claim that TSP-treated sites had statistically significantly lower erythema scores than TSP-untreated sites.
Each subject was exposed to TSP for a period of approximately 170 minutes in the study.
There were no adverse reactions reported during this study.

Reviewer's Conclusions (which may be conveyed to the sponsor):

The Poison Ivy Study:

The efficacy analysis of the Poison Ivy Study supports the claim that TSP-protected sites have statistically significantly smaller mean dermatitis score than TSP-unprotected sites 96 hours after rhus antigen application ($p<0.001$). Efficacy analysis was also performed in the following subgroups: males, females, age below 30, and age 30 or older. This analysis showed that in each of the demographic subgroups, there was a statistically significant difference in favor of TSP-protected sites with $p<0.002$.

In each of the subjects, the exposure totaled only 0.5 grams apiece for 4 hours. There were no adverse events attributable to the TSP.

The Sweat Study:

The primary efficacy analysis in the Sweat Study shows that there is a statistically significant difference in favor of TSP protection relative to the Doppler flux measurements ($p<0.001$). Primary efficacy analysis was also performed in the following subgroups: males, females, age above 40 years, and age 40 years or younger. This analysis showed that in each of the demographic subgroups, there was a statistically significant difference in favor of TSP-protected sites with $p<0.001$.

Secondary analysis of the visual scores supports the claim that TSP- protected sites had a statistically significantly lower erythema score than TSP-unprotected sites ($p<0.001$).

Each subject in the study was exposed to TSP for a period of approximately 170 minutes.
There were no adverse reactions reported during this study.

Overall Conclusions:

The primary efficacy analysis of the Poison Ivy Study supports the claim that TSP-protected sites had statistically significantly smaller dermatitis score than TSP-unprotected sites 96 hours after rhus antigen application ($p<0.001$).

The primary efficacy analysis of the Sweat Study shows that there was a statistically significant difference ($p<0.001$) in favor of TSP protection relative to the primary efficacy variable, Doppler flux measurements.

There were no adverse reactions reported during Poison Ivy Study or Sweat Study.

/S/ 11.23.99

Valeria Freidlin, Ph.D.
Mathematical Statistician, Biometrics III

/S/ NOV 26, '99

Concur: Rajagopalan Srinivasan, Ph.D.
Team Leader, Biometrics III

cc:
Archival NDA 21-084
HFD-540
HFD-540/Mr. Cross
HFD-540/Dr. Wilkin
HFD-540/Dr. Walker
HFD-540/Dr. Okun
HFD-725/Dr. Huque
HFD-725/Dr. Srinivasan
HFD-725/Dr. Freidlin
HFD-344/Dr. Carreras
Chron. (HFD-725)
This review contains 17 pages.

JAN 21 2000

STATISTICAL/CLINICAL REVIEW AND EVALUATION

ADDENDUM

NDA#: NDA 21-084

Applicant: US Army Medical and Materiel Command

Name of Drug: Topical Skin Protector (TSP)

Documents Reviewed: Volumes 1, 31-41, dated August 19, 1999

Type of Report: NDA review

Indication: Protection of skin from contact with chemical warfare agents (CWA)

Medical officer: Martin Okun, M.D. (HFD-540)

Statistical review of the NDA 21-084 was signed on November 26, 1999, before the clinical review was completed. In the Conclusions of the statistical review,

[ ]

Following a discussion with the reviewing medical officer on January 20, 2000, concerning the safety issues which were raised in the statistical review of November 26, 1999, this reviewer agrees that there is no compelling need to require

[ ]

/S/ 01.21.99

Valeria Freidlin, Ph.D.
Mathematical Statistician, Biometrics III

/S/ 1/21/99

Concur: Mohamed Al-Osh, Ph.D.
Acting Team Leader, Biometrics III