CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-084

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JAN 31 2000

Clinical Pharmacology/Biopharmaceutics Review

Topical Skin Protectant
(Polymist F5A and Fomblin Y25)
Provided as a paste in 84gm packages
NDA 21-084
Reviewer: E.D. Bashaw, Pharm.D.

Department of the Army
USAMRMC

Fort Detrick, MD
Submission Date
19-AUG-1999

Review of an NDA

I. Background

Topical Skin Protectant (TSP) is a 50-50 mixture of two high molecular weight fluorine containing polymers: Polymist F5A [aka Teflon] (polytetrafluoroethylene, PTFE) and Fomblin Y25 (perfluoroalkylpolyether, PFPE). This combination is being developed by the US Army Medical Research & Material Command (USAMRMC) as a barrier cream to protect troops in the field from exposure to nerve and other chemical warfare agents. At the present time the standard issue chemical protective gear, the so called MOPP suit (mission oriented protective posture), has potential gaps in it at the wrist, neck and pantleg where the suit meets and must overlap other uniform elements, mask, gloves, boots, etc. At these points it is possible that exposure to chemical warfare agents could occur with deleterious results. TSP is being developed to provide an inert physical barrier to chemical agent penetration at these points. Troops in the field will be provided with tubes of TSP to be applied to these areas in generous amounts after donning their MOPP gear.

II. Recommendation

While chemical warfare (CW) agents have not been used on a large scale since World War I, the potential for their use has recently increased as it is seen as the "poor man's" nuclear weapon (i.e. a weapon of mass destruction). As such the development of protective equipment and procedures has become a high priority within the military. Unfortunately, due to the extremely high lethality of these agents, real world challenge tests are not possible. The protective efficacy of this material has been tested in animal models and by the use of surrogate marker compounds in man. In both series of tests TSP was found to either inhibit or delay the penetration of the agent.

In terms of the in vivo absorption of TSP's components (PTFE and PFPE) a study was done in healthy volunteers (n=13, 8M, 5F) simulating the use of this product under field conditions in a test chamber. Urines were collected and assayed following a two day exposure of 4 hours per day, using a — NMR with a limit of quantification of 0.3ug/ml for organic fluorine and 2ug/ml for free fluorine. No fluorine was detected in the urine of the study subjects, demonstrating that the dermal absorption of TSP was minimal if any. Based on the results of this trial, and the relatively limited scope of use of this product the

product is acceptable from a biopharmaceutic standpoint for use ONLY in combination with the appropriate level MOPP gear for protection from chemical warfare agents. IT IS NOT A REPLACEMENT FOR ANY OF THE STANDARD PROTECTIVE CLOTHING AND SHOULD NOT BE VIEWED AS SUCH. In situations where CW exposure is rapid and unexpected, use of TSP should not be a hinderance to entry into proper protective clothing.

/S/ 1/25/00

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CC: NDA 21-084 (ORIG), 1/31/2000
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TSP-A Question Based Review

IV. Overview of Threat and Usage

A. What is the threat?

A United Nations report from 1969 defines chemical warfare agents as

> " ... *chemical substances, whether gaseous, liquid or solid, which might be employed because of their direct toxic effects on man, animals and plants* ... ".

The Chemical Weapons Convention defines chemical weapons as including not only toxic chemicals but also ammunition and equipment for their dispersal. Toxic chemicals are stated to be

> " ... *any chemical which, through its chemical effect on living processes, may cause death, temporary loss of performance, or permanent injury to people and animals*".

Today, thousands of poisonous substances are known but only a few are considered suitable for chemical warfare (CW). About 70 different chemicals have been used or stockpiled as CW agents during the 20th century. Today, only a few of these are considered of interest owing (see Appendix, Attachment 1) to a number of demands that must be placed on a substance if it is to be of use as a CW agent.

- A presumptive agent must not only be highly toxic but also "suitably highly toxic" so that it is not too difficult to handle.

- The substance must be capable of being stored for long periods in containers without degradation and without corroding the packaging material.
- It must be relatively resistant to atmospheric water and oxygen so that it does not lose effect when dispersed.
- It must also withstand the heat developed when dispersed.

CW agents are frequently called war gases as a result of history, even though this is technically incorrect. During the First World War use was made of chlorine and phosgene which are gases at room temperature and normal atmospheric pressure. The CW agents used today are rarely gases. Normally they are liquids or solids. However, a certain amount of the substance is always in volatile form (the amount depending on how rapidly the substance evaporates) resulting in a sufficiently high gas concentration that may become poisonous. Both solid substances and liquids can also be dispersed in the air in atomized form as aerosols. An aerosol can easily enter the body through the respiratory organs in the same way as a gas.

Some CW agents can also penetrate the skin. This mainly concerns liquids but in some cases also gases and aerosols. Solid substances penetrate the skin slowly unless they are mixed with a suitable solvent. TSP itself was not formulated to preferentially address one threat over another. It is intended to be a general protective agent against a variety of CW agents.

B. What is the current protective scheme?

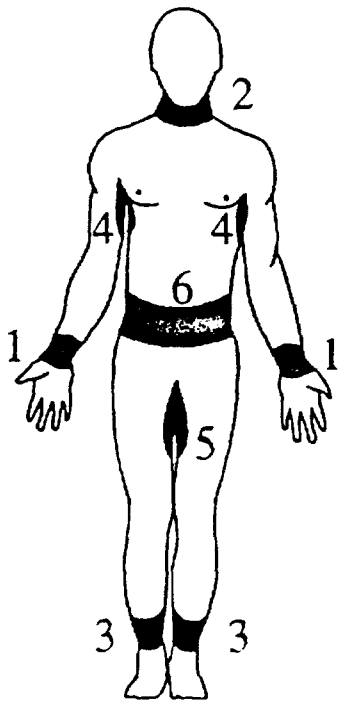
The current protective scheme used by the US Armed Forces is called MOPP for "Mission Oriented Protective Posture". This is hierarchy of protection from 0 to 4, going from no protection to full protection. The current scheme is reproduced below in Table I. (see also Attachment 2)

Table I. Wear of Chemical Protective Equipment by MOPP Level

EQUIPMENT	MOPP 0	MOPP1	MOPP2	MOPP3	MOPP4
Overgarment and Helmet Cover	Available	Worn	Worn	Worn	Worn
Vinyl Overboot	Available	Available	Worn	Worn	Worn
Mask and Hood	Carried	Carried	Carried	Worn	Worn
Gloves	Available	Carried	Carried	Carried	Worn

TSP is intended to compliment and NOT TO REPLACE any level of MOPP. It is anticipated that TSP will be applied at MOPP-1 when the protective overgarment is originally donned. TSP will be applied by the soldier to the area of the body where there are joints in the protective overgarment, i.e, the neck (mask/hood interface), wrists (jacket/glove), waist (jacket/pant), boot tops (pant/boot). In addition, TSP will be applied under the arms and in the groin area as it has been shown that mustard gas and its derivatives are particularly destructive to tissue that is in high humidity areas.

The following figure will be reproduced on each package of TSP and indicates where TSP should be applied. The order of application is indicated by number 1-6.

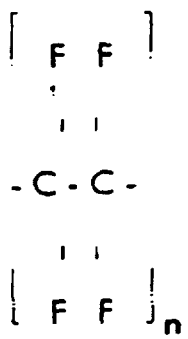


V. TSP

A. What is TSP and how does it work?

Topical Skin Protectant (TSP) is a 50-50 mixture of two high molecular weight fluorine containing polymers: Polymist F5A [aka Teflon] (polytetrafluoroethylene, PTFE) and Fomblin Y25 (perfluoroalkylpolyether, PFPE) TSP is only being developed as a barrier material for use as a protective agent against chemical warfare agents. Whether or not it is effective against biological agents (bacteria, viruses, proteins, etc) is unknown at this time and it should NOT be viewed as a general protective agent or used as a substitute for proper use of protective clothing, mask, or gloves.

Polymist F5A [aka Teflon] (polytetrafluoroethylene, PTFE)



Polymist F5A is a polymer consisting of recurring tetrafluoroethylene units. Its predominant chemical structure is $(CF_2CF_2)n$. It is a white free flowing powder consisting of discrete particles of PTFE with an average particle size of ——— Its melting point is 327° C and it is insoluble in water and common solvents. It is pH neutral and its specific gravity is 2.28g/ml.

Fomblin Y25 (perfluoroalkylpolyether, PFPE)

$$C_xF_{2x+1}\text{-}(O\text{-}CF(CF_3)\text{-}CF_2)_n\text{-}(O\text{-}CF_2)_m\text{-}O\text{-}C_yF_{2y+1}$$

Where: x, y = 1,2, or 3 and n/m >40

Variations in the values of x, y, m, and n result in Fomblin Y25 being a mixture of components with different molecular weights. The molecular weight distribution varies within certain limits to ensure specified physical and physiochemical properties; according to the applicant the relative concentrations of the different components cannot be fixed due to the nature of the production technology used. In this application it has a nominal molecular weight of 3,200.

As noted earlier TSP is a 50:50 mixture of these two fluorine containing compounds. Like most fluorine polymers, these agents are relatively chemically inert except under extreme conditions of chemical attack. They function in TSP as a barrier between the skin and any potential chemical leakage from the MOPP suit. In and of itself, TSP has no inherient protective properties beyond being a barrier. It is not a replacement for use of protective gear and should only be considered a secondary barrier.

B. How was TSP evaluated?

1.) In Vivo Absorption

a.) Study Design

Title: Potential Systemic Absorption of the Topical Skin Protectant (TSP)

Investigator: [ ]

Study Site:

Methods

This protocol is designed to assess the potential for TSP and/or its component parts to be absorbed systemically. A total of 13 healthy adult subjects (8 male and 5 female) were enrolled in the study.

Days 1 and 2 (baseline)
After meeting the eligibility criteria set forth in the protocol (designed to limit dietary fluorine intake), the subjects entered into a two day baseline period where 24hr urine collections were performed on an outpatient basis to establish their daily fluorine balance (a beverage diary was also kept).

Simulated Exposure
On days 3 and 4 each subject reported to the study unit where they were given a standard issue US Army BDU (battle dress uniform) to wear and a packet containing 84gm of TSP and instructions on how to apply the cream. Once the uniform has been put on and the TSP applied, the subjects were placed in a controlled environment chamber (65+/-2 degrees F, 50% humidity) where they were free to sit and read or study for one hour. At the end of this hour they will then don the other components of the MOPP level II outfit (except for the mask, hood and gloves). They will then be asked to walk around the chamber, up and down steps, and engage in light physical activity for an hour (water is available ad lib). At the end of the hour the subjects were allowed to remove the MOPP gear and again read or study for an additional 2 hours. After this time they were allowed to shower and leave the study unit. Twenty-four hour urine collections were obtained on these days.

Washout Phase
On day 5 the subjects again collected their urine for a final 24hr period. (An itemized and schematic representation of the study is attached in the Appendix as Atttachment 3 & 4, respectively).

b.) Analytical Methodology

The objective of this trial was to assess the potential for fluorine absorption from TSP. It was recommended by this reviewer that the Army consider the use of — NMR for sample analysis as it would provide the best potential for analytical recovery of fluorine levels as it would be able to detect both free and organically bound fluorine. The Army took the FDA up on this suggestion and has developed an analytical method for fluorine that has been validated down to 0.3 ug/ml as CF_3 and 2 ug/ml as F^-. Urine was chosen as the biologic fluid of interest as fluorine is primarily excreted in the urine and urinary toxicity is a common feature of fluorine exposure. In addition there is a regulatory history of using the urinary detection of fluorine as a pharmacokinetic assessment in the development of halogenated anesthetic agents (isoflurane, methoxyflurane, desflurane, etc.).

EDTA was added to urine collection containers at a ratio of 12-g EDTA per 3-liter urine to sequester multivalent cations (Ca^{+2}, Al^{+3}, etc.). If left untreated, inorganic fluoride in urine can complex with these cations, thus making detection by ——-NMR difficult. Addition of EDTA reduces or abolishes this complication.

NMR is a sensitive method for the detection of both organic and inorganic fluoride present in samples. As implemented in this trial approximately 2-mL from each of the 5 collection days for every subject were removed from the labeled urine containers for NMR analysis. NMR urine samples were prepared by the addition of at a ratio of 2:1 (urine to D:O) to provide a lock signal for NMR spectral data collection. was performed using a spectrometer operating at a magnetic field strength of 7.05 Tesla and a spectrometer frequency for fluorine of 288.345 MHz. A sweep width of 20,000 Hz was used, since it enabled observation of NMR resonances for both inorganic fluoride (F-) and organically bound fluorine. Acquisition time for each transient was set at 0.750 seconds using a 90° pulse width (11 microseconds) with no delay between transients. Four thousand transients (NT=4000), requiring approximately 1 hour, were routinely collected for each sample. A priori a signal-to-noise (S/N) ratio of at least 3/1 was established to justify peak analysis. If an observation was made of apparent peaks having a S/N of less than three, then these peaks were validated by re-analysis of the sample using a greater number of transients (32,000) to ascertain if S/N could be enhanced at a rate proportional to (NT). Reproduced below is a representative spectrum from a spiked urine sample from one of the subjects.

Figure 6.2.1-1 Spectrum of Urine Sample Collected from Subject 6 on Day 1 to Which Was Added Known Amounts of CF_3COONa and NaF for Analysis as a Mixed Standard

Pulse Sequence:
Solvent: Urine:
Sweep Width:
Acquisition Time:
Pulse Width:
Delay Time:
Transients:

This figure shows the NMR spectrum at full spectral width of one of the mixed standards containing CF_3COONa and NaF. The chemical shifts of NMR peaks are expressed as parts per million (ppm) which is the difference in hertz between the reference frequency and the peak of interest divided by the spectrometer frequency. Peak heights and areas are in relative units. Conditions for NMR spectral acquisition are listed above and are explained in the associated text.

The single NMR peaks at chemical shifts of 57.90 parts per million (ppm) and at 13.36 ppm are characteristic of resonances for CF3COONa and for NaF, respectively.

c.) Analytical Validation

Standard urine samples containing sodium trifluoroacetate (CF3COONa) and sodium fluoride (NaF) were prepared at concentrations from 4 ug/mL to 160ug/mL for CF3COONa and from 10ug/mL to 750 ug/mL for NaF. These samples were used to check instrument performance and to validate linearity of the method. Under these conditions, the resonances for CF_3 appeared as a sharp peak with negligible fluctuation in

peak position (0.1 **ppm**[1]) from one urine sample to the next. F appeared as a broader peak with a fluctuation in its position of —— **ppm** among samples. Plots of fluorine concentration as CF3COONa or NaF versus peak areas from these spectra yielded straight lines (correlation coefficients were always > 0.96). From these plots, limits of quantitation established —— and —— as the limits of quantitation of the method without secondary dilution of the controls. Additional dilutions of the lowest controls samples yielded limits of detection of —— for CF3 and —— for F for analyses conducted by collection of 4,000 transients. For 32,000 transients, the limits of detection were 0.3ug/mL F as CF_3 and 2 ug/mL as F-. Attached in the appendix are the following figures:

Fig 1. Low resolution NMR spectrum of a standard sample.
Fig 2. High resolution (32,000 transients) NMR spectrum of Fig 1 sample centered on F peak.
Fig 3. High resolution (32,000 transients) NMR spectrum of Fig 1 sample centered on the CF_3 peak.
Fig 4. NMR spectrum of TSP itself solubilized in DMSO
Fig 5. Low resolution NMR spectrum of subject 6, day 4 sample (following two days of exposure to TSP).
Fig 6. Representative standard curves for CF_3 concentration.
Fig 7. Representative standard curves for F concentration.

Based on the information provided by the applicant and our review of the data (i.e., submitted spectrums, standard curve data, etc.) it appears that the analytical methodology was sensitive and reproducible for both organic and inorganic fluoride. The procedure of using a two stage analysis of samples (i.e., low resolution and confirmatory high resolution) is an acceptable method given that analysis of a single sample with 4,000 transients took an hour.

d.)Results

Examination of the data generated from this study indicates that TSP was essentially non-absorbed. No positive samples were identified from the urine of the individuals exposed to TSP in this study using 4,000 transients. In light of this finding the samples, being intact, were re-analyzed using 32,000 transients. Again no fluorine was detected in any of the samples, indicating that any fluorine, if present was at levels below 0.3ug/mL as CF_3 and 2 ug/mL as F-.

2.) In Vivo Protective Challenge
a.) Test Agents

A series of in vivo protective challenges were done using TSP and surrogates for CW agents. CW agents could not be used in vivo due to their extreme toxicity even in minute amounts (see Attachment 1 for LD_{50}'s. In discussion with the FDA throughout the development of this project a number of surrogate compounds were suggested and

[1] **PPM here means part per million SPECTRAL SHIFT not ppm as in 1ug/ml**

subsequently evaluated by the applicant. Specifically rhus antigen (the antigen present in poison ivy) and methyl nicotinate were used in the pivotal clinical trials that are reviewed in the medical review by Dr. Okun. These antigens while useful in that they provoke a cutaneous response even after low doses, they are, however, not ideal surrogates. One of the problems with these agents is that they are structurally unrelated to CW agents in terms of either molecular weight or solubility.

[ ]

3.) In Vitro Challenge

In vitro challenges were conducted using a combination of live CW agents with animals and CW detector tape[2] and human skin testing. Normally for the animal and detector tape challenges thickened soman was applied to an area that had previously been treated with TSP. The challenges lasted, on average, for four hours, and TSP under a variety of conditions was able to either completely protect the skin from exposure or to delay the time and rate of penetration significantly compared to control animals. However, it should be noted that for soman exposure 100% and for VX exposure 67% of all animals registered some drop in plasma acetylcholinesterase activity. (*please see the non-clinical pharmacology review by Dr. Lynda Reid for details on these studies*)

In man, the applicant has provided results of in vivo testing looking at the penetration of TSP into the skin using an elemental x-ray technique and scanning electon microscopy.

> Von Tersch, Robert L.; Hamilton, Tracey; and Petrali, John (1997) Analysis of the Dermal Penetration of Perfluoropolyethers through Human Skin. U.S. Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, MD.

In this study the sponsor applied TSP to various skin samples obtained primarily from cosmetic surgery procedures. Approximately 200mg of TSP was placed on the surface of full thickness skin samples from which the adipose layer had been removed. The skin was subsequently placed in petri dishes containing 10ml of phosphated buffered saline (PBS) to keep the tissue moist over a contact time of 1 hour.

The skin samples were then prepared for analysis via elemental x-ray dispersion microanalysis by excision of non-treated skin and slicing the treated area down the middle to provide a cross section of tissue for bombardment with x-rays. In general the results of this analysis showed no penetration of Fluorine beyond the stratum corneum.

[2] CW Detector Tape changes in color in response to exposure to CW agents. It is used in the field as a frontline warning system.

See Fig. VIII. This figure is representative of the LOW quality of the submitted documentation of the materials. [According to the accompanying text fluorine containing areas (TSP) should be a bright orange color.] While not definitive in nature, even the low quality of the presented material supports the conclusion that TSP is not absorbed systemically.

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NDA 21-084

Attachments

Chemical Warfare Agent Characteristics

Agent Type	Chemical Agent; Symbol Chemical Structure	Molecular Weight	State @ 20°C	Odor	Vapor Density (Air = 1)	Liquid Density (g/cc)	Freezing/ Melting Point (°C)	Boiling Point (°C)	Vapor Pressure (mm/Hg)	Volatility (mg/m³)	Heat of Vaporization (cal/g)	Decomposition Temperature (°C)	Flash Point	Stability	Median Lethal Dose (LD_{50}) (mg-min/m³)	Median Incapacitating Dose (ID_{50})	Eye & Skin Toxicity	Rate of Action	Physiological Action	Detoxification Rate	CWC
NERVE	Tabun; GA $C_5H_{11}N_2O_2P(CH_3)(CN)(OC_2H_5)$	162.3	Colorless to brown liquid	Fairly fruity; none when pure	5.63	1.073 at 25°C	-6	240	0.037 @ 20°C	610 @ 25°C	79.86	150	78°C	Stable in steel at normal temperatures	15,000 by skin (vapor) or 1500 (liquid); 70 inhaled	<50 inhaled	Very high	Very Rapid	Cessation of breath – death may follow	Slight, but definite	1.A.(1)
	Sarin; GB $CH_3P(O)(OCH(CH_3)_2)F$	140.1	Colorless liquid	Almost none when pure	4.86	1.0887 at 25°C	-56	158	2.9 @ 25°C; 2.10 @ 20°C	22,000 @ 25°C; 16,000 @ 20°C	80	150	Non-flammable	Stable when pure	10,000 by skin (vapor) or 1700 (liquid); 35 inhaled	25 inhaled	Very high	Very rapid	Cessation of breath – death may follow	cumulative	1.A.(1)
	Soman; GD $CH_3P(O)(OCH(CH_3)C(CH_3)_3)F$	182.179	Colorless liquid	Fruity; camphor when impure	6.33	1.0222 at 25°C	-42	198	0.4 @ 25°C	3,900 @ 25°C	72.4	130	High enough not to interfere w/ military use	Less stable than GA or GB	2,500 by skin (vapor) or 350 (liquid); 35 inhaled	25 inhaled	Very high	Very rapid	Cessation of breath – death may follow	Low - essentially cumulative	1.A.(1)
	(Cyclo-sarin); GF $CH_3P(O)F(OC_6H_{11})$	180.2	Liquid	Sweet; musty; peaches; shellac	6.2	1.1327 at 20°C	-30	239	0.044 @ 20°C	436 @ 20°C	80.8	—	94°C	Relatively stable in steel	2,500 by skin (vapor) or 350 (liquid); 35 inhaled	25 inhaled	Very high	Very rapid	Cessation of breath – death may follow	Low	1.A.(1)
	VX $(C_2H_5O)(CH_3)P(O)S(CH_2CH_2N(CH(CH_3)_2)_2)$	267.38	Colorless to amber liquid	None	9.2	1.0083 at 20°C	below -51	298	0.0007 @ 20°C	10.5 @ 25°C	78.2 @ 25°C	Half-life of 36 hr at 150	159°C	Relatively stable at room temperature	150 by skin (vapor) or 5 (liquid); 10 inhaled	35 by skin (vapor) or 3.5 (liquid); 10 inhaled	Very high	Very rapid	Produces casualties when inhaled or absorbed	low - essentially cumulative	1.A.(3)
	V_X ("V sub x")	211.3	Colorless liquid	None	7.29	1.062 at 20°C	—	258	0.007 @ 25°C; 0.004 @ 20°C	75 @ 25°C; 46 @ 20°C	67.2	—	—	Relatively stable	—	—	Very high	Rapid	Produces casualties when inhaled or absorbed	low - essentially cumulative	
BLISTER	Distilled Mustard, HD $(ClCH_2CH_2)_2S$	159.08	Colorless to pale yellow liquid	Garlic or horseradish	5.4	1.268 @ 25°C; 1.27 @ 20°C	14.45	217	0.072 @ 20°C	610 @ 20°C	84	149 - 177	106°C, ignited by large explosive charges	Stable in steel or aluminum	900 (inhaled); 5,000 by skin (vapor) or 1,400 (liquid)	500 (skin), 100 (inhaled); 25 (eyes or nose)	Eyes very susceptible, skin less so	Delayed: hours to days	Blisters; destroys tissue; injures blood cells	Very low – cumulative	1.A.(4)
	Nitrogen Mustard, HN-1 $(ClCH_2CH_2)_2NC_2H_5$	170.08	Dark liquid	Fishy or musty	5.9	1.09 @ 20°C	-34	194	0.24 @ 25°C	1,520 @ 20°C	77	Decomposes before boiling is reached	High enough not to interfere w/ military use	Adequate	1,500 (inhaled); 20,000 (skin)	200 by eye; 9,000 by skin	Eyes susceptible to low concentration; skin less so	Delayed 12 hours or longer	Blisters; affects respiratory tract, destroys tissue; injures blood cells	Not detoxified - cumulative	1.A.(4)
	Nitrogen Mustard, HN-2 $(ClCH_2CH_2)_2NCH_3$	156.07	Dark liquid	So spicy (low concentrations); Fruity (high)	5.4	1.15 @ 20°C	-65 to -60	75 at 15mmHg	0.29 @ 20°C	3,580 @ 25°C	78.8	Below boiling, polymerizes with heat generation	High enough not to interfere w/ military use	Unstable	3,000 (inhaled)	<HN-1 & >HN-3, 100 by eye	Toxic in eyes, blisters skin	Skin - delayed 12 hrs or more, Eyes - faster than HD	Similar to HD; bronchopneumonia possible after 24 hours	Not detoxified, cumulative	1.A.(4)
	Nitrogen Mustard; HN-3 $N(CH_2CH_2Cl)_3$	204.94	Dark liquid	None, if pure	7.1	1.24 @ 20°C	-37	256	0.0109 @ 25°C	131 @ 25°C	74	Below boiling point	High enough not to interfere w/ military use	Stable	1,500 (inhaled); 10,000 by skin (est.)	200 by eye; 2,500 by skin (est.)	Eyes very susceptible, skin less so	Serious effects same as HD; minor effects sooner	Similar to HN-2	Not detoxified - cumulative	1.A.(4)
	Phosgene oxime/dichloroformoxime; CX COCl/NOH	113.94	Colorless solid or liquid	Sharp, penetrating	3.9	-	35 to 40	53 -54 at 26mmHg	11.2 @ 25°C (solid); 13 @ 40°C (liquid)	1,800 @ 20°C	101 at 40°C	Decomposes slowly at normal temperature	—	Decomposes slowly	3,200 (inhaled)	very low	Powerful irritant to eyes and nose, liquid corrosive to skin	Immediate effects on contact	Violently irritates mucous membranes, eyes, and nose; forms wheals rapidly	—	
	Lewisite; L $ClCH=CHAsCl_2$	207.36	Colorless to brownish	Vortex, may resemble geraniums	7.1	1.90 @ 20°C	-10	190	0.394 @ 20°C	4,480 @ 20°C	NA at 0°C to 190°C	>100	None	Stable in steel and glass	1,200–1,500 (inhaled); 100,000 (skin)	<300 by eye; >1,500 to 2,000 by skin	Severe eye damage, skin less so	Rapid	Similar to HD; plus may cause systemic poisoning	Not detoxified	1.A.(3)
	Mustard-Lewisite mixture; HL	190.4	Dark, oily liquid	Garlic or	6.5	1.66 @ 20°C	-25.4 (pure)	<190	0.248@ 20°C	2,730 @ 20°C	58 to 84	>100	Very high not to interfere w/ military use	Stable in lacquered steel	15,000 (inhaled) >10,000 (skin)	200 by eye; 1,500 to 3,000 by skin	Very high	Prompt stinging; blistering agent (about 12 hours)	Similar to HD; plus may cause systemic poisoning	Not detoxified	1.A.(4); 1.A.(3)
	Phenyldichloroarsine; PD $C_6H_5AsCl_2$	222.91	Colorless liquid	None	7.7	1.65 @ 20°C	-30	252 to 253	0.033 @ 25°C	390 @ 25°C	68	Stable to boiling point	High enough not to interfere w/ military use	Very stable	2,800 (inhaled)	10 as vomiting agent; 1,800 as blister	633 mg-min/m³ produces eye casualty; less toxic to skin	Immediate eye effects, skin effects in 30 to 60 minutes	Irritates; causes nausea, vomiting and blisters	Probably rapid	
	Ethyldichloroarsine; ED $C_2H_5AsCl_2$	174.88	Colorless liquid	Fruity, but biting; irritating	6.0	1.66 @ 20°C	-65	156	2.09 @ 30°C	20,000 @ 20°C	52.8	Stable to boiling point	High enough not to interfere w/ military use	Stable in steel	3,000–6,000 (inhaled); 100,000 (skin)	6 to 10 by inhalation	Vapor harmful on long exposure; liquid blisters +L	Immediate irritation; delayed blistering	Damages respiratory tract, affects eyes; blisters, can cause systemic poisoning	Rapid	
	Methyldichloroarsine; MD CH_3AsCl_2	160.86	Colorless liquid	None	5.5	1.636 @ 20°C	-55	133	7.78 @ 20°C	74,800 @ 20°C	49	Stable to boiling point	High enough not to interfere w/ military use	Stable in steel	3,000 - 5,000 (est.)	25 by inhalation	Eye damage possible, blisters less than HD	Immediate irritation; delayed blistering	Irritates respiratory tract, injures lungs and eyes; Causes systemic poisoning	Rapid	
BLOOD	Hydrogen cyanide; AC HCN	27.02	Colorless gas or liquid	Bitter almonds	0.930 @ 20°C	0.687 @ 20°C	-13.3	25.7	742 @ 26°C; 612 @ 20°C	1,080,000 @ 25°C	233	>63.8	0°C, ignited 65% of time when decomposed by military shells	Stable if pure; can burn on explosion	Varies widely with concentration	Varies with concentration	Moderate	Very rapid	Interferes with body tissues' oxygen use; accelerates rate of breathing	Rapid: 0.017 mg/kg/min	3.A.(2)
	Cyanogen chloride; CK CNCl	61.46	Colorless gas or liquid	Pungent, biting; Can go unnoticed	2.1	1.18 @ 20°C	-6.9	12.8	1,000 @ 25°C	2,600,000 @ 20°C	103	100	None	Tends to polymerize; may explode	11,000	7,000	Low; lacrimatory and irritating	Very rapid	Chokes, irritates, causes slow breathing rate	Rapid: 0.02 to 0.1 mg/kg/min	3.A.(2)
	Arsine; SA AsH_3	77.93	Colorless gas	Mild garlic	2.69	1.34 @ 20°C	-116	-62.5	11,100 @ 20°C	30,800,000 @ 20°C	83.7 @ -62.5°C	280	Below decomposition temp., mixtures of air may explode spontaneously	Not stable in unoxidized metal containers	8,000	2,500	None	Delayed 2 hours to 11 days	Damages blood, liver, and kidneys	Low	
CHOKE	Phosgene; CG $COCl_2$	98.92	Colorless gas	New-mown hay; green corn	3.4	1.37 @ 20°C	-128	7.6	1,173 @ 20°C	4,300,000 @ 7.6°C	58	800	None	Stable in steel if dry	3,200	1,600	None	Immediate to 3 hr, depending on conc.	Damages and floods lungs	Not detoxified - cumulative	3.A.(1)
	Diphosgene; DP $ClCOOCCl_3$	197.85	Colorless gas	New-mown hay; green corn	6.8	1.65 @ 20°C	-57	127-128	4.3 @ 20°C	45,000 @ 20°C	67.4	300 to 350	None	Unstable; tends to convert to CG	3,200	1,600	Slightly lacrimatory	Immediate to 3 hr, depending on conc.	Damages and floods lungs	Not detoxified - cumulative	3.A.(1)
VOMIT	Diphenylchloroarsine; DA $(C_6H_5)_2AsCl$	264.5	White to brown solid	None	Forms little vapor	1.387 @ 60°C	41 to 44.5	333	0.0038 @ 45°C	46 @ 45°C	96.6	300	350	Stable if pure	15,000 (est.)	12 (>10 minutes)	Irritating; not toxic	Very rapid	Like cold symptoms, plus headache, vomiting, nausea	Moderate	
	Adamsite; DM $(C_6H_4)_2AsCl_2NH(C_6H_4$	277.97	Yellow to green solid	None	Forms little vapor	1.65 (solid) @ 20°C	195	410	Negligible	Negligible	80	Melting point	None	Stable in glass or steel	Variable, avg. 11,000	22 (1 min.); 6 (60 min. exposure)	Irritating, relatively not toxic	Very rapid	Like cold symptoms, plus headache, vomiting, nausea	Rapid in small amounts	
	Dewylaylyarsenazine; DC $(C_6H_5)_2AsCN$	268.8	White to pale solid	Bitter almond-garlic mixture	Forms little vapor	1.3338 @ 36°C	31.8 to 38	350	0.0002 @ 20°C	2.6 @ 20°C	71.1	300 (26% decomposed)	Low	Stable at normal temperatures	10,000 (est.)	30 (30 sec); 20 (9 min. exposure)	Irritating; not toxic	More rapid than DM or DA	Like cold symptoms, plus headache, vomiting, nausea	Rapid	
Incapacitating	BZ	337.4	White crystal	None	11.6	Bulk 0.81 solid; Crystal 1.33	167.5	320	0.03 @ 70°C	9.8 @ 70°C	62.9	begins at 170°C	246°C	Adequate	200,000 (est.)	112	—	Date; ed. 1 to 4 hours depending on exposure	Fast heart beat, vomiting, dry mouth, blurred vision, stupor, harassing random activity	—	3.A.(3)
TEAR	Chloroacetophenone; CN $C_6H_5COCH_2Cl$	154.59	Solid	Apple blossoms	5.3	1.318 (solid) @ 20°C	54	248	0.0041 @ 20°C	34.3 @ 20°C	98	Stable to boiling point	High enough not to interfere w/ military use	Stable	7,000 to 14,000	80	Temporarily severe eye irritation, mild skin irritation	Instantaneous	Causes tearing, irritates eyes and respiratory tract	Rapid	
	Chloroacetophenone in Chloroform; CNC	128.17	Liquid	Chloroform	4.4	1.40 @ 20°C	0.33	variable, 60 to 247	127 @ 20°C	Indeterminate	n/a	Stable to boiling point	None	Adequate	11,000 (est.)	80	Temporarily severe eye irritation, mild skin irritation	Instantaneous	Cause tearing, irritates eyes and respiratory tract	Rapid	
	Chloroacetophenone and Chloropicrin in Chloroform; CNB	141.78	Liquid	Flypaper	~5	1.47 @ 20°C	2	variable, 60 to 247	76 @ 20°C	610,000 @ 20°C (includes chloroform)	n/a	Stable to boiling point	None	Adequate	11,400	80	Irritating, not toxic	Instantaneous	Vomiting and choking agent as well as a tear agent	Slow because of effect of PS	
	Chloroacetophenone in Benzene and Carbon Tetrachloride; CNB	119.7	Liquid	Benzene	~4	1.14 @ 20°C	-7 to -30	variable 75 to 247	variable; mostly solvent vapor	Indeterminate	n/a	>247	>4.44°C	Adequate	11,000 (est.)	80	Temporarily severe eye irritation, mild skin irritation	Instantaneous	Powerfully lacrimatory	Rapid	
	Bromobenzylcyanide; CA $BrC_6H_4CH_2CN$	196	Yellow or solid liquid	Scented fruit	6.7	1.47 @ 25°C	25.5	Decomp. goes at 242	0.011 @ 20°C	118 @ 20°C	78.5 @ 20°C	90 to 242	None	Fairly stable in glass, lead, or pigment	8,000 to 11,000 (est.)	30	Irritating, not toxic	Instantaneous	Irritates eyes and respiratory passages	Rapid in low dosage	
	Bromobenzylmalonitrile; CS $CC_6H_4CH_2C(CN)_2$	188.5	Colorless solid	Pepper	—	1.04 @ 20°C	93 to 95	310 to 315	0.00034 @ 20°C	0.71 @ 25°C	63.6	—	197°C	Stable	61,000	10 to 20	Highly irritating, not toxic	Instantaneous	Highly irritating, not toxic	Rapid	
	CR $(C_6H_5)_2C(NH)CH$	195.25	Yellow powder in solution	Burning sensation	6.7	—	72	335	0.00009 @ 20°C	0.63 @ 25°C	—	—	188°C	Stable	—	0.15	Highly irritating, not toxic	Instantaneous	Irritates skin, eyes, nose, and throat	Moderate	
	Chloropicrin; PS CNO_2Cl_3	164.38	Liquid	Stinging; pungent	5.6	1.66	-69	112	18.3 @ 20°C	168,000 @ 20°C	—	>400	Not flammable	Adequate; unstable in light	2,000	8	Highly irritating	Instantaneous	Acts as tear, vomiting and choking agent	Slow	3.A.(1)

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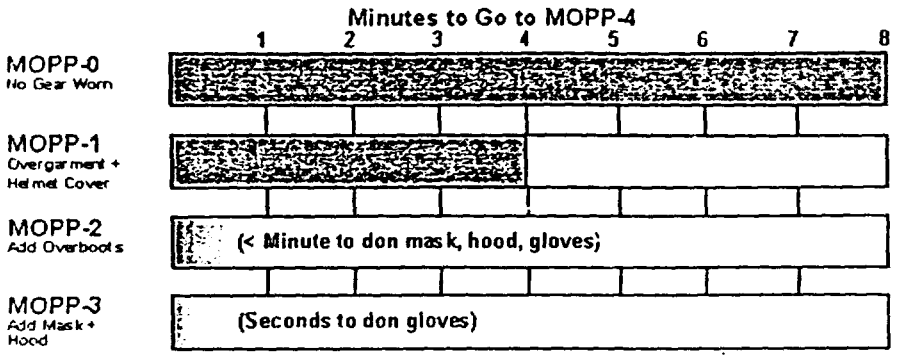
Attachment (1)

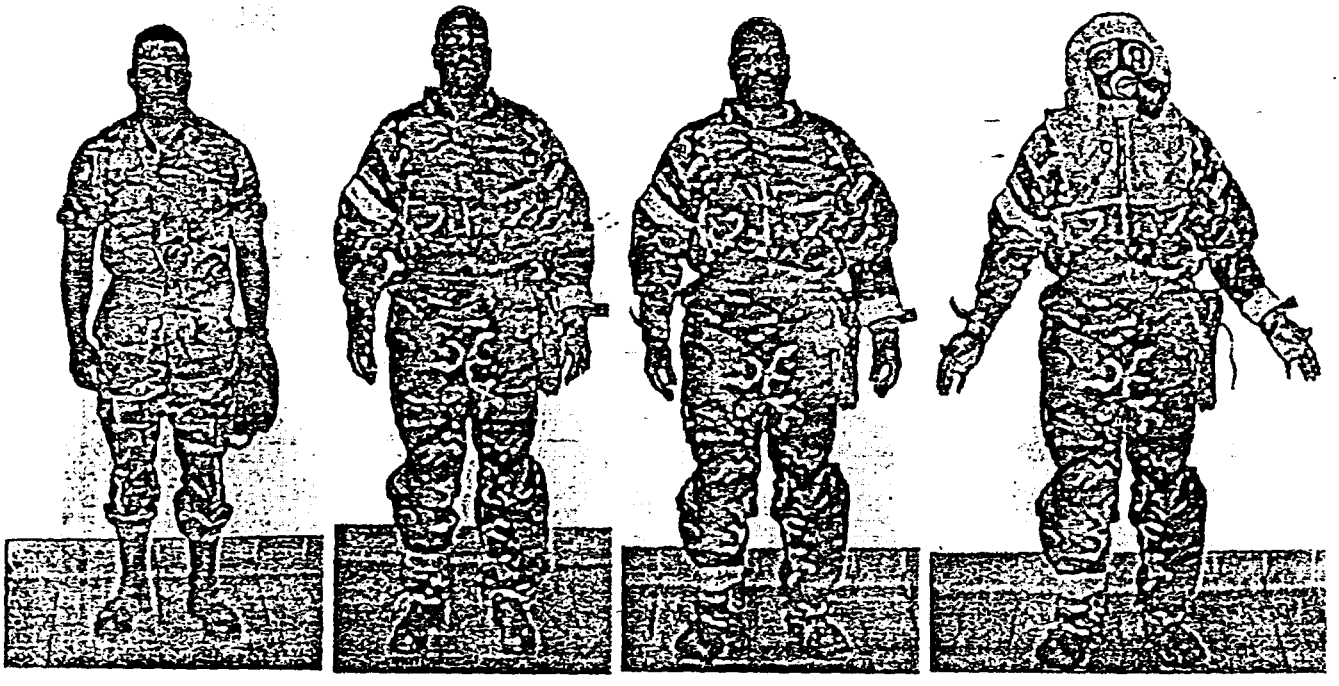
BEST POSSIBLE COPY

Attachment (2)

MOPP Level and Time to Go to MOPP-4



CPE Worn at Each MOPP Level



MOPP-0 MOPP-1 MOPP-2 MOPP-3

APPEARS THIS WAY
ON ORIGINAL

Attachment (3)

5335SS
Revision: 0
Effective: 12/4/98

SBJID# _____
Date__/__/__

BEST POSSIBLE COPY

Data entry 1st 2nd
Reviewed by Date
PI Review Date

Topical Skin Protectant (TSP) Test Session 1 Session 2
(Circle Current Session)

☐ Subject Arrives at MRI Time:_____

Subject is:

☐ Given the package of topical cream used by the army. Tag# _____
☐ Instructed on the application of the topical cream.
☐ Issued Army clothing supplied by the Army.
☐ Directed to the bathroom to apply the cream and change into Army issued clothing. Experimenter:_____ Time:_____

☐ Empty topical cream package is returned to the experimenter.

☐ Subject is escorted to the environmental chamber.
Experimenter:_____ Room#:_____

☐ Once the subject is in the room, the 4 hour test period begins.
Experimenter:_____ Time:_____

☐ Subject relaxes for one hour.

☐ Subject puts on mop suit and begins light exercise for one hour.
Experimenter:_____ Time:_____

☐ After one hour of light exercise, subject removes mop suit and subject can relax and read for two hours.
Experimenter:_____ Time:_____

☐ After four hours, from beginning of test period subject leaves environmental chamber.
Experimenter:_____ Time:_____

☐ Subject is escorted back to change area, takes shower and changes to street clothing.
Experimenter:_____ Time:_____

☐ Time subject left building:_____ Experimenter:_____ Time:_____

☐ **Deviations:**

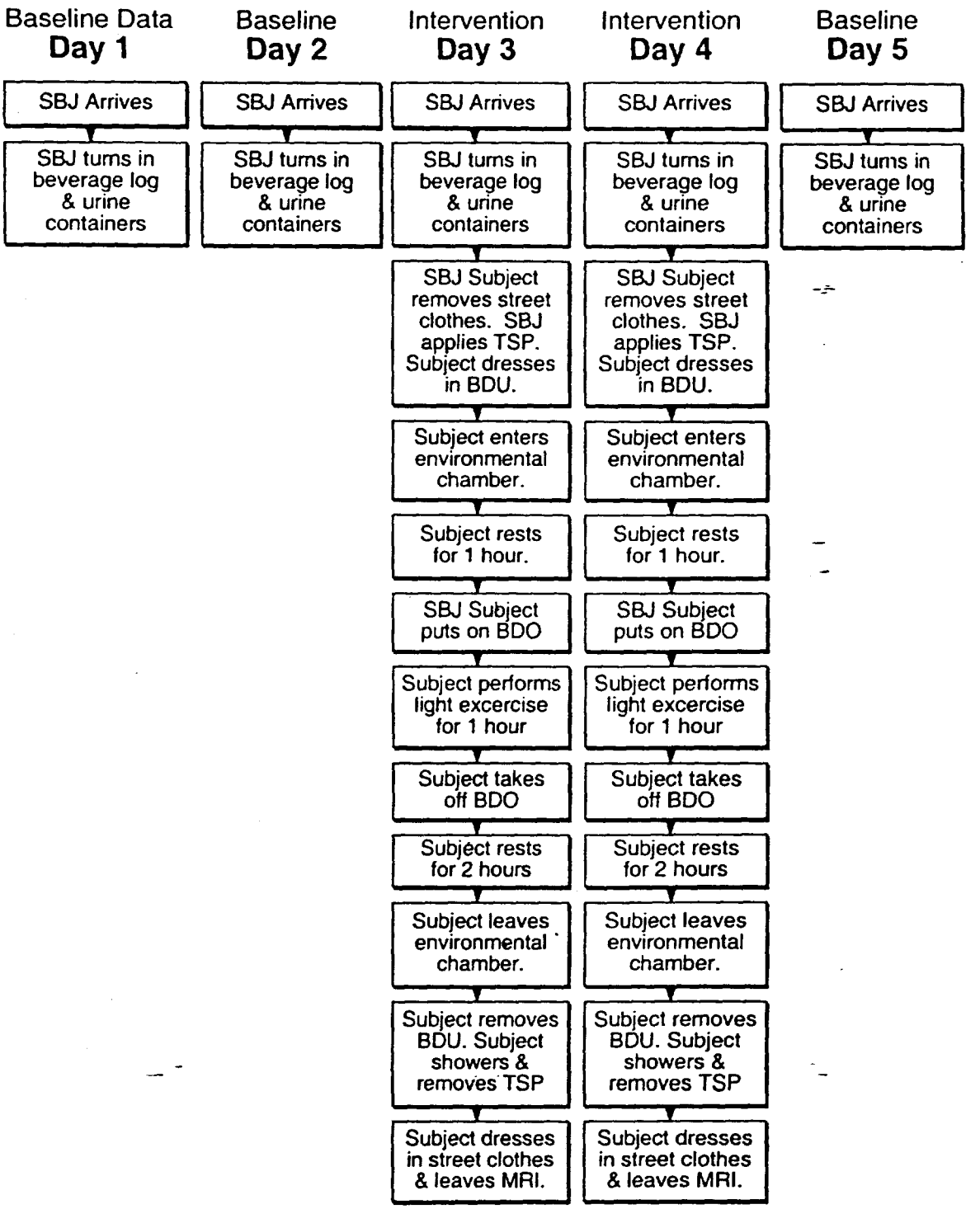
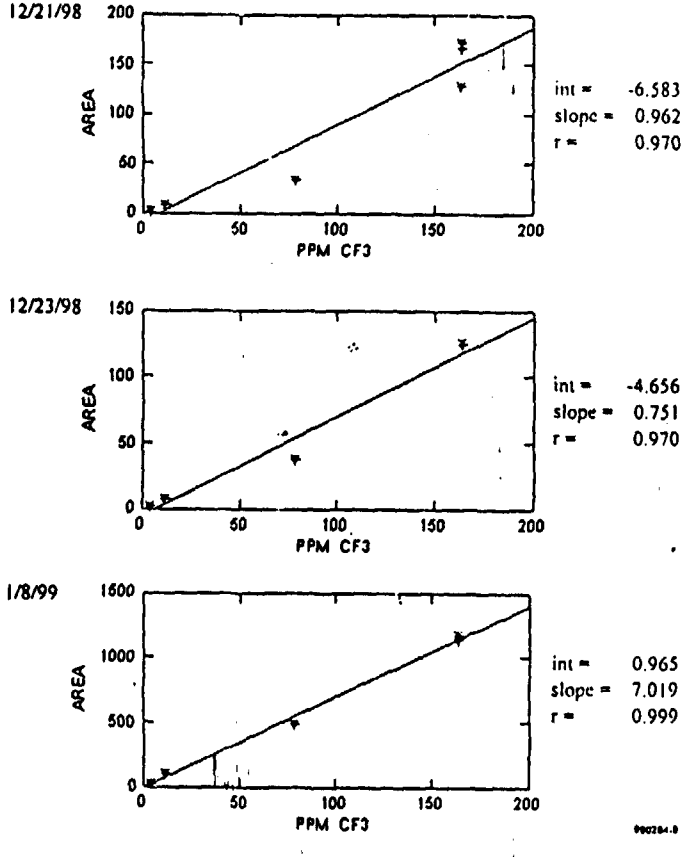


Chart 1. Flow chart of subject TSP application and activities.

WITHHOLD 2

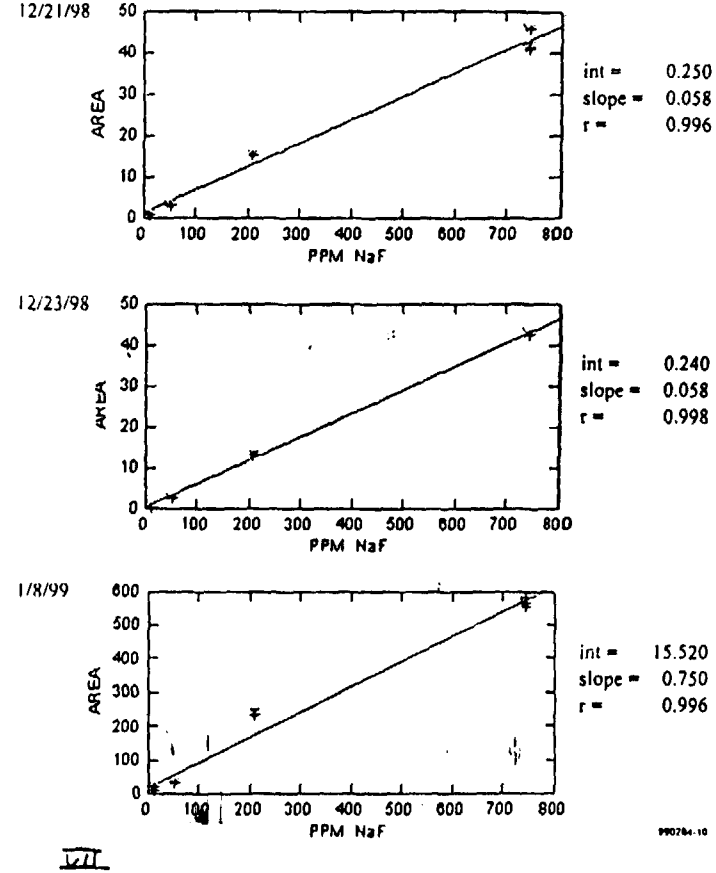
Peak Area vs ppm CF_3



VI

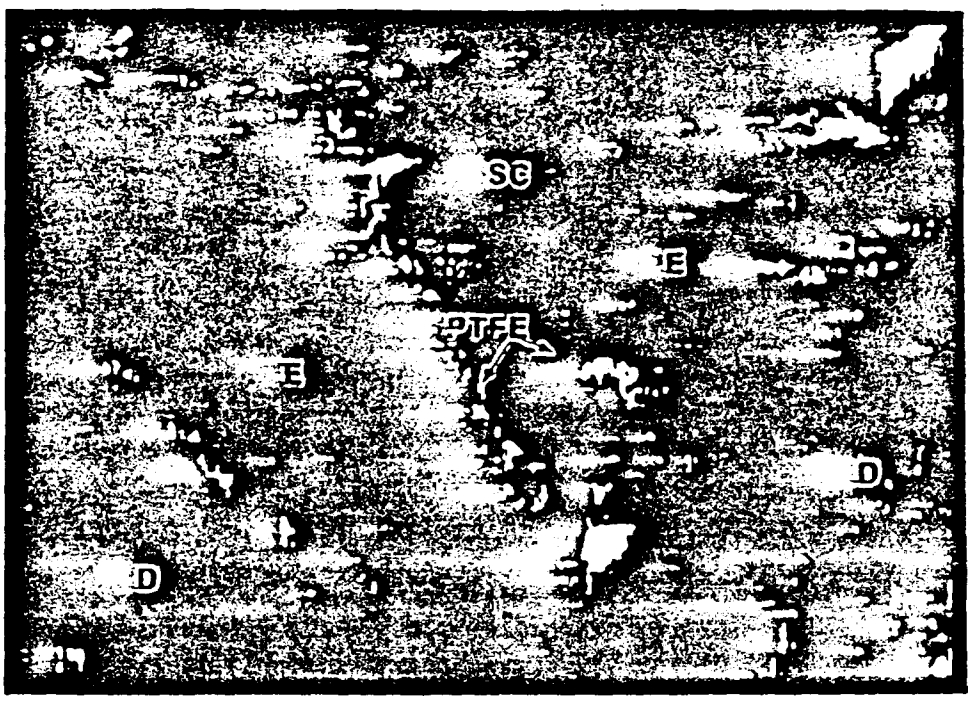
Figure 6. This figure illustrates separate linearity determinations for CF_3COONa, among many such determinations that were performed. The variation in best-fit parameters is evident. See also Figure 7.

Peak Area vs ppm NaF

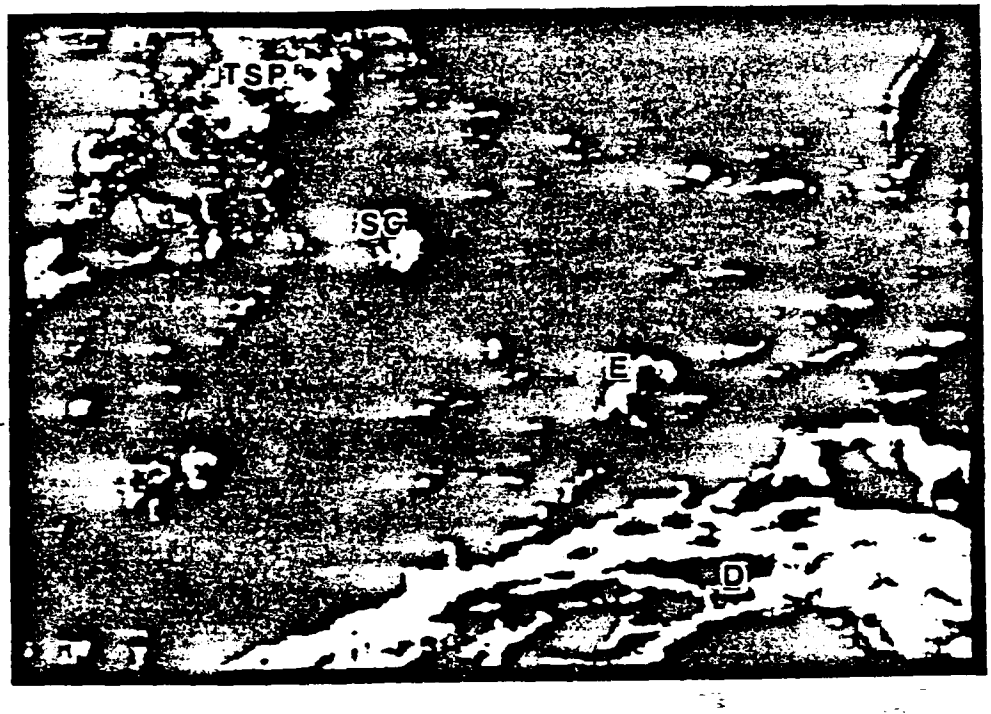


VII

Figure 7. This figure illustrates separate linearity determinations for NaF, among many such determinations that were performed. The variation in best-fit parameters is evident. See also Figure 6.



VIII
Figure 7. X-ray microanalysis SEM map of TSP ICD #2289 on human skin for one hour displaying clumps of fluorinated material only on the surface. Tissue processed as outlined in Materials and Methods. (D = dermis, E = epidermis, SC = stratum corneum, TSP = topical skin protectant)



IX
Figure 8. X-ray microanalysis SEM map of TSP ICD #2289 on human skin for one hours displaying clumps of fluorinated material only on the surface. Tissue processed as outlined in Materials and Methods. (D = dermis, E = epidermis, SC = stratum corneum, TSP = topical skin protectant)