RESEARCH LABORATORIES
EDGEWOOD ARSENAL
Edgewood Arsenal, Maryland 21010

RCC2.950308.041

QUARTERLY PROGRESS REPORT

1. RESEARCH PLAN: Number - 12,101 Report Date - Jul - Sep 1973
Project 1W062116AD2102

Title -

Effect of Environment on Penetration of Toxic Agent and Irritant Chemicals Through Skin

2. PROGRESS: Include summary of each supporting contract.

The skin penetration of scopolamine in the base form was studied. The localized sweat inhibition technique was used to measure the penetration of scopolamine which was applied to the neck of 4 volunteers. Two volunteers received 1 mg of scopolamine and two volunteers received 2 mg of scopolamine which was dissolved in ethyl alcohol.

Scopolamine inhibited sweating locally on one man after two hours; no central effects were noted on this man. The other three men did not show sweat inhibition until tested again the next day at 24 hours.

It appears that scopolamine base does not penetrate skin as rapidly as EA 3834B even when greater quantities are applied. The results continue to reinforce the concept of wide variation between individuals in skin permeability.

3. SIGNATURE:

E. G. Cummings

Principal Investigator E. G. CUMMINGS, Ph.D.
Applied Physiology Group, Medical Physiology Branch

Date 18 Sept 73

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17 Mar 66

RESEARCH LABORATORIES
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QUARTERLY PROGRESS REPORT

1. RESEARCH PLAN: Number - 12101 Report Date - 27 Mar 74
Project AD2102

Title -

Effect of Environment on Penetration of Toxic Agent and Irritant Chemicals Through Skin

2. PROGRESS: Include summary of each supporting contract.

When a drop of EA 3834 B dissolved in alcohol is applied to the skin at time T_o, the rate of local sweating remains unchanged until time T_1 when the rate begins to decline. The decline continues to time T_2 when a minimum sweat rate is reached at the rate of insensible perspiration. Significant differences were found between forearm (6 subjects) and upper arm (5 subjects) in respect to time (T_2-T_o), 220 $\pm$ 20 minutes for forearm and 84 $\pm$ 20 minutes for upper arm, and in respect to time (T_2-T_1), 124 $\pm$ 27 minutes for forearm and 41 $\pm$ 17 minutes for upper arm. Results for the lower leg (5 subjects) were similar to those for forearm. Since inhibition of sweating is evidence of the penetration of the compound through epidermis to the cholinergic nerve ending at the eccrine sweat gland, the presumed site of action, the results demonstrate that EA 3834 B penetrates the skin faster on the upper arm than on the forearm.

Three subjects have been used to obtain data from neck skin and in the next quarter this series of experiments will be completed. Also the effect of solvents on the penetration of atropine, scopolamine and EA 3834 B will be investigated.

3. SIGNATURE:

E G Cummings

Principal Investigator EDMUND G. CUMMINGS, PH.D.
Applied Phys Gp

FRANCIS N. CRAIG, Ph.D.
Chief, Med Phys Br

Date 29 Mar 74

RESEARCH LABORATORIES
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QUARTERLY PROGRESS REPORT

1. RESEARCH PLAN: Number - 12,101 Report Date - June 1974
Project AD2102

Title -

Effect of Environment on Penetration of Toxic Agent and Irritant Chemicals Through Skin

2. PROGRESS: Include summary of each supporting contract.

Penetration of a droplet of EA 3834B through neck skin was studied to make comparisons with other skin areas reported in the previous quarter. Sweating remains unchanged from the time of application T_0 to the time T_1 when sweat rate begins to decline. Sweat rate declines to time T_2 when a minimum rate is reached. A significant difference (95% level) was found between upper arm (5 subjects) and neck (6 subjects) with respect to time T_1-T_0, 76 minutes for neck and 43 minutes for upper arm; and in respect to time T_3-T_0, 131 minutes for neck and 84 minutes for upper arm. The slopes of the sweat rate decline with time from T_2 to T_3 were not significantly different. The sweat rates for the neck were much higher than the sweat rates from the upper arm, 5.01 to 1.11 g/m^2/min.

The results are contrary to experience with VX, which penetrated neck skin more easily than arm skin. The difference is as yet unexplained, but it may be that because of the greater sweat rate of neck than arm, a larger concentration is required to inhibit sweating, and more time is required for the concentration to accumulate after penetration.

3. SIGNATURE: E G Cummings

Principal Investigator EDMUND G. CUMMINGS, Ph.D.
Applied Physiology Gp

Date June 25, 1974

RESEARCH LABORATORIES
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Edgewood Arsenal, Maryland 21010

QUARTERLY PROGRESS REPORT

1. RESEARCH PLAN: Number - 12101M Report Date -1 Apr - 30 Jun 72
PROJECT NO: 1B062116AD21-02
Title - Effect of Environment on the Penetration of Toxic Agents and Irritant Chemicals THRU Skin

2. PROGRESS: Include summary of each supporting contract.

In February 1971, application of 1.5 mg of EA 3834A in 1 percent aqueous solution to an area of 3 x 3 cm on the volar surface of the forearm at a room temperature of 41°C had no effect within one or two hours; after 24 hours local sweating was inhibited by about one-half, as measured by resistance hygrometry. In May 1972 3 mg of EA 3834 in ethyl alcohol was applied to an area of 3 x 3 cm on the neck. In the three volunteers tested at 41°C, sweating shut down on the spot of application within two hours. The increased rate of penetration is attributed to the change in dose and point of application.

Future work is planned to measure the rate of penetration of glycolates through the skin by means of the local effect on sweating and comparison with the intravenous dose required to produce the same effect.

Manuscripts are in preparation on:

a. Skin penetration of glycolates measured by inhibition of local sweating.

b. Skin penetration of CS measured by changes in cutaneous circulation.

3. SIGNATURE:

Principal Investigator

Date 27 June 1972

EDMUND G. CUMMINGS, Ph.D.
Applied Physiology Section
Clinical Research Branch

RESEARCH LABORATORIES
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Edgewood Arsenal, Maryland 21010

QUARTERLY PROGRESS REPORT

1. RESEARCH PLAN: Number - 12101M Report Date - 1 Jul-30 Sep 72
PROJECT NO: 1B062116AD21-02
Title - Effect of Environment on the Penetration of Toxic Agents and Irritant Chemicals Thru Skin

2. PROGRESS: Include summary of each supporting contract.

Experimental work on skin penetration has been temporarily transferred to research plan titled "Percutaneous Absorption of Agents" with Samuel Cucinell,MD, as principal investigator in which the effects of heat, and hydration on the cutaneous penetration of EA 3834 are being investigated. This work on EA 3834 penetration has been an outgrowth of RP 12101M in which the cutaneous penetration of glycolates had been measured by their effect on localized sweat inhibition.

Work on determining the limitations of the dual channel resistance hygrometry system for measuring the effect of drugs on sweat rate is proceeding by the measurement of humidity responses to variations in flow rate of the air stream.

Manuscripts in preparation:

a. Skin Penetration of Glycolates Measured by Inhibition of Local Sweating.

b. Skin Penetration of CS Measured by Changes in Cutaneous Circulation.

3. SIGNATURE:

Principal Investigator

Date
30 September 1972

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RESEARCH LABORATORIES
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Edgewood Arsenal, Maryland 21010

QUARTERLY PROGRESS REPORT

1. RESEARCH PLAN: Number - 12101M Report Date - 1 Jan - 31 Mar 73
PROJECT NO: 1W062116AD21-02
Title - Effect of Environment on Penetration of Toxic Agents and Irritant Chemicals THRU Skin

2. PROGRESS: Include summary of each supporting contract.

Inactive except for development work on a new full range humidity sensor of sulfonated polystyrine to replace the present series of fractional range lithium chloride sensors.

The cost of using central effects to detect penetration of skin by glycolates is too great to permit study of all the variables. Local suppression of sweating will be used as an indicator of skin penetration for studies of the dose response relation at various skin sites under various environmental conditions as soon as reports of previous work have been completed.

A report on skin penetration of glycolates based on local sweat suppression is nearing completion. Experiments have begun to compare the penetration of time of EA 3834B through three different skin areas, i.e., forearm, palm and back. It is proposed that the effect of solvents upon skin penetration of EA 3834B be investigated in the next FY using this technique with the goal of selecting a feasible agent solvent system.

3. SIGNATURE:

Principal Investigator

Date
31 March 1973

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QUARTERLY PROGRESS REPORT

1. RESEARCH PLAN: Number - 12101M Report Date - 1 Apr - 30 Jun 73
PROJECT NO: 1W062116AD21-02
Title - Effect of Environment on Penetration of Toxic Agents and Irritant Chemicals THRU Skin

2. PROGRESS: Include summary of each supporting contract.

Local suppression of sweating as an indicator of glycolate skin penetration appears to be a promising technique for estimating the percutaneous incapacitating effectiveness.

The penetration time of EA 3834B through skin of the forearm, upper arm and lower leg was measured and the projected doses required to produce incapacitation were estimated. This estimation was based on previous experimentation with neck skin and was based on the hypothesis that the longer the time required for sweat inhibition, the larger the percutaneous dose required for central effect. These results are being verified under research plan 12003.

To induce sweating, men were placed in a 105°F room where they walked on a treadmill at 3 mph for 10 minutes; subsequently they sat for the duration of the test. After sweating had stabelized (20-30 min) a surface application of the glycolate was made and the time required for sweating to be inhibited was recorded. Sweating was measured by resistance hygrometry. Time for sweat inhibition to begin, which is the assumed time for the glycolate to penetrate to the receptor site, was as follows: upper arm - 42 min, forearm - 96 min and lower leg - 85 min. These values are means from 5 men. The duration of local sweat inhibition, tested on 2 men, lasted at least 48 hours but had disappeared at 144 hours when the men were retested.

The technique will be continued, probably using other glycolates.

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30 June 1973

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