UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MAR 30 1982

MEMORANDUM

DATE: MAR 8 1982

SUBJECT: (1) Registration of Dow Corning 5700 on fabrics. Reg #34292-1
(2) Review of Dermal Absorption study in rabbits.
CASWELL#892B

FROM: Henry Spencer, Ph. D. 3/9/82.
Review Section #1
Toxicology Branch/HED (TS-769) 3/9/82

TO: John Lee, PM 31
Registration Division (TS-767)

Registrant: Dow Corning Corp.

Material: Dow Corning 5700
antimicrobial agent 3-(trimethoxysilyl) propyl dimethyl octadecylammonium chloride.

Conclusions and Recommendations:

1. TOX Branch concludes the absorption study as presented by the registrant may have been incorrectly calculated. TOX Branch recalculation does indicate that the chemical passes the dermal barrier.

2. TOX Branch concludes that the test material does leach from 100% cotton fabric at low pH (see memo of R. Landolt dated Jan. 18, 1980).

3. TOX Branch further recommends that only the following requested items be included for registration:

   a) toweling - 100% cotton
   b) bed sheets - if not 100% cotton
   c) outerwear apparel - 100% cotton

Toxicology Branch recommends deleting the following uses (see memo of H. Spencer, 9/23/81).

a) men's underwear - only 100% cotton.
b) womens hosiery - only 100% cotton i.e. upper pantyhose portions and childrens panties and underwear.
c) any fabric of 100% cotton which might be used for long periods in intimate contact with the skin. i.e. 100% cotton bras, diapers.

TOX Branch notes that there are several studies submitted by Dow Corning in support of the DC5700 material. These studies have been previously reviewed by TOX Branch. However, these studies are of IBT origin and pending validation as of this memo.

4. Further mutagenicity testing is warranted considering the possibility that:

If registered, male gonads will be exposed to the material, DC5700.

The epithelium and dermis of the testicles, a very absorbant surface of the integument presents little resistance to the absorption of applied materials.

5. TOX Branch concludes that in order to extend the uses to include underwear, and those type items deleted in par 3 above.

   a. Long term exposure studies for tumorigenicity, mutagenicity and metabolism, may be necessary.

   b. The metabolism study should mimic as closely as possible the route of exposure to find the t 1/2 in the body, and be able to delineate the metabolites, if any.

   (Toxicology Branch would consider the subcutaneous route most appropriate here).

6. Further background tissue values should be submitted in order to utilize the tissue data.

Review of Study:

Percutaneous Absorption of Dow Corning 5700 Antimicrobial agent in Rabbits.

Test Material:

Dow Corning 5700 Antimicrobial agent, 3-(trimethoxysily) propyldimethyl ($1^{14}C$) octadecyl ammonium chloride (Sp. Act. = 7.98 mCi/g. Lot No. 1202-244; assay No. 80-197033). Purity was greater than 98.8%.

Test Animals:

Male and female New Zealand White rabbits (2.5-3.0 kg) from Langshaw Farms, Augusta, Michigan were used in this study after a ten day screening and observation period following receipt of the animals.

Methodology:

The test animals were kept at 20-24°C and 50-60 percent relative humidity.

The study utilized 2 groups of 6 animals each (3 males and 3 females). One group received the test material i.v. via an ear vein as 69.4 micrograms/100 microliters while the 2nd group received the test material by percutaneous application over a 16cm^2 area of the back. 66.5 micrograms of ^{14}C DC5700 was applied to the hair-free area as an aqueous solution from a syringe. The surface was dried quickly by gentle blowing, and covered by a cotton cloth wrapping taped to the hair for the entire 10 day study period.

After administration by either route, the test animals were individually housed in stainless steel metabolism cages. Standard laboratory rabbit ration and water were provided ad lib.

Collections:

Urine and feces were collected at 24 hr. intervals for 10 days excepting the first 12 hours. Collected Samples were frozen until ^{14}C was estimated.

After ten days on study the animals were exsanguinated under methoxyflurane anesthesia. Plasma was prepared.

Whole liver, kidneys, lung, spleen, brain, gonads as well as samples of skeletal muscle and peritoneal fat were removed, weighed and frozen for ^{14}C determination.

Brain was macerated prior to sampling for ^{14}C. Skin application sites were excised and totally digested for ^{14}C determination by scintillation.

^{14}C Determation:

1. Urine and plasma was sampled in duplicate 1 ml samples added to 15 ml of Aquasol scintillation fluid.

2. Fecal samples were dried and homogenized in a blender. Duplicate samples (about 250 mg) were oxidized in a model Ox-300, Harvey Instruments Sample Oxidizer to recover $^{14}CO_2$-and counted in 15 ml of monoethanolamine and Dowanol E.M. (3:7 v/v).

3. Tissue Samples:

Representative, duplicate samples (100-200 mg) of each tissue were digested with 1 ml of Protosol at 55-60°C for 18 hr. Further digestion was carried out on incompleted reactions. Digested samples were counted using 15 ml of Econofluor. The dermal site of application was counted using 100 microliter of the digestant in 15 ml of counting solution.

Cotton collar (cloth bandage) digestion was completed with 70% sulfuric acid at 37°C for 2 hr. using, 50 ml per each 3-5 g of material. Counting used 2 ml of digestant diluted with 15 ml of Aquasol.

Radioactivity Measurement:

A model 6892 liquid scintillation spectrophotometer from Tracor Analytic was used to estimate ^{14}C.

Total counts that were at least 2x above background were used in calculations. Background values were not reported in the finished report.

Results:

No signs of systemic toxicity or gross pathological alterations were noted in any organs or tissues at necropsy.

Individual data on urine and fecal samples were presented for both i.v. and dermally treated groups. Urinary excretion varied on day 1 through day 10 following i.v. treatment. Animal #2804 F, i.v. group and #2809 M, percutaneous group were excluded due to errors in treatment. However #2801 F, percutaneous, should also have been excluded since the collar came off on day 8. The increased numbers of counts in the urine and feces from day 2 through the end, of the study suggest that the test animal may have had access to the treated area.

As evidenced by the urinary and fecal excretory values in the i.v. treated group, TOX Branch finds that approximately 47% more, on the average after 10 days, is excreted by the fecal route compared to the urinary route.

Ratios of total fecal to urinary excretion after 10 days were variable between sexes and males appeared to excrete more of the compound by the fecal than the urinary route.

i.v. Group		Urine Total microgram	Fecal Total microgram	Fecal/Urinary ratio
Females	2802	10.7	20.5	1.9
	2803	23.6	11.6	0.5
Males	2814	2.1	13.3	6.3
	2815	5.4	7.8	1.4
	2817	5.0	15.9	3.2

Table IV in the report does indicate that the organs will contain ^{14}C activity 10 days after an i.v. dose preferentially in the liver. The kidney and lung contained similar amounts of ^{14}C activity. The gonads did not show ^{14}C activity in the report.

The values presented by the registrant on the percutaneous experimentals indicate no material was left in the tissues after 10 days and from 75.9% to 87.4% of the applied dose remained either on the collar or the treated skin.

Note:

Toxicology Branch does not consider the background + 50 counts to be reasonable without some rationale for using such a large deviation from the mean.

As a consequence, Toxicology Branch requested the raw data by which to check (and/or recalculate) if possible, the values used in the report.

Upon obtaining the raw data, one could see the replicates were not duplications of the same sample but were in fact two different samples thus allowing great variations in the cpms obtained.

The feces ^{14}C was counted as a non colored gas in the cocktail. The cocktail background was available and should not have been as high as 104 (mean $\pm$ 50 cpm).

Therefore recalculation for background of the feces in the percutaneous group could allow a count of 61 (53 mean $\pm$ 2 S.D.) providing a 95% C.L.

In addition, the first one to two days of urine counts may reasonably be considered as a urine background for an individual animal in the percutaneous group. These values $\pm$ 2 S.D. also have been used as appropriate backgrounds.

When the above two derived backgrounds were used in the recalculations,

it was found that:

1) One male, #2811, excreted only 0.61% of the total dose in the urine late in the study.

2) One female, #2805 excreted only 1.63% of the total percutaneous dose in the feces commencing on day 6. No C^{14} was found in the urine.

3) A male, #2808, excreted a total of 3.91% of the total dose by both routes again starting on day 5 of fecal collections and on day 7 of urine collection.

By recalculation of the i.v. group of animals with respect to the ^{14}C excreted in the feces, variable amounts of ^{14}C as % of dose were seen which were different enough from those values reported in the study to question the methods of calculation.

The registrant methodology of calculation cannot be followed with respect to tissues (no tissue, urines or feces backgrounds were present).

This reviewer considers the quench correction by channels ratio adequate, but the backgrounds were necessary for subtraction prior to quench correction.

Since only fecal values were able to be used in both the i.v. and percutaneous groups for comparison, those results are presented using the background of 61 (mean ± 2 SD).

i.v. group	fecal percentage excreted	
#2802	27.42	
#2803	22.24	
#2804	14.11	
#2814	24.47	
#2815	15.36	
#2817	19.80	
mean	20.56%	the mean of 20.56% of the total dose is excreted by the fecal route.

per. cut. group	micrograms excreted calculated		estimated absorbed dose-microgram
#2805	1.085	÷0.2056 =	5.27
#2808	2.288		11.12

Toxicology Branch concludes that: 1) control animal tissue backgrounds will be necessary in order to evaluate possible ^{14}C activity in the p. cut. and i.v. group tissues.

2) Since ^{14}C was excreted following percutaneous application the tissues should be further recalculated with additional control tissue background counts.

It is necessary to have some idea of concentrations is those tissues prior to the completion of a hazard assessment.

3) An untreated cloth collar digestant background should also be submitted.

4). Supplemental date

Samples for comparison of Registrant findings with those of the Toxicology Branch reviewer on p. cut. treatment follow:

Differences of background C.P.M.
Registrant background $\pm$ 50 $\cong$ 100
Tox. Branch background $\pm$ 2 SD $\cong$ 61
$(53.5 \pm 7.2) = \cong 61$

Feces.	Registrant #2805 CPM -100	Tox. Br. CPM-61	Registrant #2802 CPM -100	Tox. Br. CPM -61
Day 1	0	0	0	0
Day 2	0	0	0	0
Day 3	0	0	0	0
Day 4	0	0	0	0
Day 5	0	0	0	2
Day 6	0	2/4	0	21
Day 7	0	2/0	0	24
Day 8	0	9/8	0	20
Day 9	0	20/13	0	12
Day 10	0	18/7	0	5
	0	1.63%	0	3.44%

Since background CPM from untreated tissues and urines were not present, only the fe ces here could be used. However a second method of using the day 1 urine as background for that individual animal was applied. Which would not be applicable to the i.v. dosed group.

Registrant background ≅ 100+
Tox. Br. background varied per animal on day 1

Urines Background	Registrant #2805 PM-100		Tox. Br. CPM-82	Registrant #2802 CPM-100	Tox. Br. CPM-87
Day 1	0		0	0	0
Day 2	0		0	0	0
Day 3	0	NOT IN URINE	0	0	0
Day 4	0		0	0	0
Day 5	0		0	0	0
Day 6	0		0	0	0
Day 7	0		0	0	2.5
Day 8	0		0	0	0
Day 9	0		0	0	12
Day 10	0		0	0	9
Day 11	0		0	0	5.5
	0% of dose		0% of dose	0% of dose	0.47% of dose