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WASHINGTON, D.C. 20460

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OCT 13 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA ID No. 34291-1; Dow Corning 5700 Antimicrobial Agent, Containing 3-(Trimethoxysilyl) propyldimethyloctadecyl Ammonium Chloride as the Active Ingredient; Review of Subchronic Dermal and Genotoxicity Studies

DP Barcode: D208081
Case: none
Submission: none

Tox. Chem. No. 892B
P.C. Code No. 107401
MRID 413394-01, -02, -03
MRID 413533-01, -02

HED Project # 0-0562
Record # 258412

FROM: Edwin R. Budd, Toxicologist
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THRU: Karen Hamernik, Ph.D., Section Head
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Health Effects Division (7509C)

10/5/94

KH 10/7/94

I. ACTION REQUESTED

Review the following studies, all of which were performed using Dow Corning 5700 hydrolysate, containing 3-hydroxysilyl) propyldimethyloctadecyl ammonium chloride as the test material.

A. Developmental toxicity study, rats (range-finding); IRDC (Mattawan, MI); # 416-067; December 14, 1989; MRID # 413394-01

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B. 14-Day subchronic dermal study, rats (range-finding); Dow Corning Corp. (Midland, MI); file # 3933-18; September 27, 1989; MRID # 413394-02

C. 90-Day subchronic dermal study, rats; Dow Corning Corp. (Midland, MI); file # 3933-19; December 18, 1989; MRID # 413394-03

D. Mutagenicity--gene mutation in mammalian cell cultures (L5178Y/TK +/- mouse lymphoma forward mutation assay); Hazleton Laboratories America (kensington, MD); study # HLA-10864-0-431; December 26, 1989; MRID # 413533-01

E. Mutagenicity--supplemental studies to gene mutation in mammalian cell cultures (L5178Y/TK+/- mouse lymphoma forward mutation assay); Hazleton Laboratories America (Kensington, MD); study # HLA-10864-0-431 SUP; January 2, 1990; MRID # 413533-02

II. CONCLUSIONS

A. The range-finding developmental toxicity study on rats (MRID # 413394-01 and # 414380-02) has previously been reviewed in Toxicology Branch I (TB-I). The definitive developmental toxicity study on rats which followed the range-finding study (MRID # 414380-03) also has been reviewed in TB-I. See memorandum from John Redden to Jim Wilson/John Lee (PM Team # 31, RD), dated July 10, 1991 and memorandum from John Redden to Valdis Goncarovs (Antimicrobial Branch, RD), dated April 1, 1993. The definitive study is currently classified as Core Minimum and satisfies the requirement for a developmental toxicity study in one species (Guideline 83-3(a)). The test material in these studies was Dow Corning 5700 Hydrolysate, 3-(hydroxysilyl) propyldimethyloctadecyl ammonium chloride.

Note--the definitive study is identified as follows:

Developmental toxicity study, rats; IRDC (Mattawan, MI); # 416-068; February 28, 1990; MRID # 414380-03

B. The 14-day range-finding and 90-day definitive subchronic dermal studies on rats (MRID # 413394-02 and # 413394-03) have been reviewed. In the definitive study, the NOEL for both males and females was $\geq$ 1000 mg/kg/day, the highest dose tested (limit dose). The definitive study is classified as Core Minimum and satisfies the requirement for a 90-day subchronic dermal toxicity study (Guideline 82-3). The Executive Summary for the definitive study is presented below and a DER (for both studies) is attached. The test

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material in these studies was Dow Corning 5700 Hydrolysate, 3-(hydroxysilyl) propyldimethyloctadecyl ammonium chloride.

EXECUTIVE SUMMARY: In a 90-day subchronic dermal toxicity study on rats, DC 5700 hydrolysate, suspended in propylene glycol vehicle, was applied dermally to groups of 10 male or 10 female Sprague Dawley rats at dosage levels of 0 (sham control), 0 (vehicle control), 100, 500 or 1000 mg/kg/day for 6 hours/day, 5 days/week for 90 days. The test material or vehicle was applied to all groups at a constant dose volume of 5 ml/kg.

No treatment related effects on mortality, signs of toxicity, behavior, body weights or food consumption were observed. No differences in hematology and clinical chemistry parameters were noted between control and test groups. Gross necropsies, organ weights and histopathological examinations did not reveal any effects attributable to the test material. **The NOEL for both males and females in this study is ≥ 1000 mg/kg/day, the highest dose tested (limit dose).**

This study is classified as Core Minimum and satisfies the requirement for a 90-day subchronic dermal toxicity study (Guideline 82-3).

C. The mutagenicity study, gene mutation in mammalian cell cultures (L5178Y/TK +/- mouse lymphoma forward mutation assay) (MRID # 413533-01), has been reviewed. In this study, the results were negative (i.e. no increase over controls in mutant colonies). The study is classified as "Acceptable". The Executive Summary for this study is presented below and a DER is attached. The test material in this study was Dow Corning 5700 Hydrolysate, 3-(hydroxysilyl) propyldimethyloctadecyl ammonium chloride.

EXECUTIVE SUMMARY: In a single trial, mouse lymphoma (L5178Y) cells were exposed to test article up to levels of precipitation (62.5 ug/ml and higher) and/or cytotoxicity (6 ug/ml/-S9; 23 ug/ml/+S9) with **no increase over control in mutant colonies (TK+ to TK-).**

D. The supplemental studies (MRID # 413533-02) to the above mutagenicity study were not evaluated, but were summarized in an ADDENDUM (on page 5) to the DER for the mutagenicity study described above. The results of the supplemental studies do not affect the results of or alter the interpretation of the above mutagenicity study (MRID # 413533-01).

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cc: Dona Canales/Virginia Dietrich
Product Manager Team 51
Special Review and Reregistration Division (7508W)

TB194:DC570006.104

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Reviewed by: Edwin R. Budd, M.A. Budd 8/23/94
Review Section III, Toxicology Branch I, HED (7509C)
Secondary Reviewer: Karen Hamernik, Ph.D., Section Head R.L. 8/30/94
Review Section III, Toxicology Branch I, HED (7509C)

DATA EVALUATION REPORT 011290

Study Type: 90-Day Subchronic Dermal Toxicity Study, Rats (With 14-Day Range-finding Study) EPA Subdivision F Guideline 82-3

Test Material: DC 5700 Hydrolysate

Chemical Name: 3-(Hydroxysilyl)propyloctadecyldimethyl Ammonium Chloride

Tox. Chem. No.: 892B

PC Code No.: 107401

MRID No.: 413394-03 (90-day study, 87 pages)
413394-02 (14-day range-finding study, 15 pages)

Study Title: A 90-Day Subchronic Dermal Toxicity Study of Dow Corning 5700 Hydrolysate in Rats

Testing Laboratory: Toxicology Department
Dow Corning Corporation (Midland, Michigan)

File No.: 3933-19

Authors: M.F. Dwane, D.W. King, W.H. Siddiqui, and M.A. Zimmer

Study Director: W.H. Siddiqui

Report Date: December 18, 1989

Sponsor: Dow Corning Corporation (Midland, Michigan)

EXECUTIVE SUMMARY: In a 90-day subchronic dermal toxicity study on rats, DC 5700 hydrolysate, suspended in propylene glycol vehicle, was applied dermally to groups of 10 male or 10 female Sprague Dawley rats at dosage levels of 0 (sham control), 0

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(vehicle control), 100, 500 or 1000 mg/kg/day for 6 hours/day, 5 days/week for 90 days. The test material or vehicle was applied to all groups at a constant dose volume of 5 ml/kg.

No treatment related effects on mortality, signs of toxicity, behavior, body weights or food consumption were observed. No differences in hematology and clinical chemistry parameters were noted between control and test groups. Gross necropsies, organ weights and histopathological examinations did not reveal any effects attributable to the test material. **The NOEL for both males and females in this study is ≥ 1000 mg/kg/day, the highest dose tested (limit dose).**

This study is classified as Core Minimum and satisfies the requirement for a 90-day subchronic dermal toxicity study (Guideline 82-3).

I. DETAILED REVIEW

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A. Test Material: DC 5700 Hydrolysate

Description: Dow Corning Q9-5700 hydrolysate (DC 5700 hydrolysate), 3-(Hydroxysilyl)propyloctadecyldimethyl Ammonium Chloride, Lot No. BN029263, TX No. 89-0200-05, fine white powder. Note: DC 5700 hydrolysate is made by adding water to DC 5700 Antimicrobial Agent, collecting the precipitate, washing it with water and acetone, drying it, and grinding it into a fine, white powder. It contains 81.1% of the active ingredient. The remaining ingredients are impurities. (see FAX from M.G. Hales; Dow Corning, Midland, Michigan; dated June 10, 1992).

Dosage Form: The test material was suspended in propylene glycol USP. Three suspensions (low, middle and high doses) were prepared daily and kept on a magnetic stirrer until dosing was completed.

B. Test Animals: Rats, CD (Sprague Dawley), males and females

Description: Obtained from Charles River (Portage, Michigan), acclimated 7 days prior to dosing.

Environment: Individually housed in stainless steel, wire mesh bottom cages; standard environmental conditions in a room controlled for 22 ± 3° C, 30-70% relative humidity, 12 hours light/dark cycle; animals were given Purina Certified Rodent Chow #5002C and fresh water ad libitum.

C. Study Design: The animals were assigned to treatment groups as shown below.

Treatment Group	Dose Level (mg/kg/day)	Number of Animals Males	Females
Sham Control[1]	0	10	10
Vehicle Control[2]	0	10	10
DC 5700 hydrolysate	100	10	10
DC 5700 hydrolysate	500	10	10
DC 5700 hydrolysate	1000	10	10

[1] No test material or vehicle was applied to these animals prior to wrapping.

[2] These animals were treated with propylene glycol (5 ml/kg) prior to wrapping.

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Test material or vehicle control was applied to the clipped dorsal surface of each rat for 6 hours/day, 5 days/week for 90 days. The dose volume was kept constant at 5 ml/kg. Following application, "a porous gauze dressing, held with non-irritating tape, was covered with a cotton cloth bandage and secured with adhesive tape to the marginal hair. The material remained in contact with the skin throughout the daily six hour exposure period. Following this time, the animals were unwrapped and washed with tap water to remove all residual 5700 hydrolysate" (quoted from page 8 of the study report). Doses were adjusted weekly according to the most recent body weights.

Selection of Dose Levels: In a preliminary 14-day range-finding study in rats (Dow Corning Corporation, Project No. 3933-18, September 27, 1989, MRID # 413394-02), rats were treated in the same manner as described above with DC 5700 hydrolysate at dose levels of 0 (vehicle control), 100, 500 or 1000 mg/kg/day. Each group contained 2 male and 2 female rats. No mortalities or signs of toxicity were observed in any of the groups, no differences in mean body weights or food consumption were noted between control and test groups, and no treatment-related effects were noted at gross necropsy. It was concluded that the same dose levels would be appropriate for the 90-day study since 1000 mg/kg/day is considered to be a limit dose.

D. Quality Assurance and GLP Compliance Statements:

Quality Assurance (QA) inspections were conducted throughout the study. A QA and GLP compliance statement, signed and dated December 18, 1989, was included in the study report.

E. Statistical Evaluation:

"Statistical comparison between vehicle control and test groups were carried out where applicable. Body weights and food consumption, hemogram, blood chemistry values, and absolute and relative organ weights were analyzed statistically by a one-way analysis of variance. The sham control means were by a one way analysis compared with the vehicle control using Dunnett Multiple T-test (Steel and Torrie, 1960). The level of significance was $P<0.05$." (quoted from page 10 of the study report).

F. Observations and Results:

1. Clinical Signs: All animals were observed 2 times each week day for mortalitiy, signs of toxicity and behavioral abnormalities. Mortality checks were conducted on weekends.

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Results: No treatment related deaths occurred during the study. One low dose female rat, sacrificed during week 11, had a cranial mass which was subsequently determined to be a malignant lymphoma. Due to the lack of a dose response, this isolated finding was not considered to be treatment related. No other overt signs of toxicity or behavioral abnormalities were noted in any of the control or test groups.

2. Body Weights: Body weights for all animals were recorded weekly and continued up to termination of the study at 90 days.

Results: Weekly group mean body weights for male and female rats are presented in Tables I and II respectively (tables copied from pages 15-16 of the study report). The male vehicle control group consistently and progressively weighed less than the male sham control and test groups throughout the study. By week 4, the male vehicle control group weighed about 5% less and by week 10 about 10% less than the other male groups. The difference, however was not statistically significant at any time. Similarly decreased body weights were not observed for the female vehicle control group when compared to the other female groups. Further, no other differences in group mean body weights were observed between male control and test groups or between female control and test groups. No ready explanation for the decreased body weights in the male vehicle control group was evident, but it is clearly not treatment related since these animals received no test material.

3. Food Consumption: Food consumption by individual rats was recorded weekly.

Results: Weekly group mean food consumption data for male and female rats are presented in Tables III and IV respectively (tables copied from pages 17-18 of the study report). Very slightly decreased food consumption (not significant) was observed for the male vehicle control group compared to the male sham control and test groups, but the difference was probably insufficient to account for the difference in body weights described above for this group. No other differences in group mean food consumption were observed between male control and test groups or between female control and test groups.

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4. Ophthalmoscopic Examinations: Ophthalmoscopic examinations were stated to have been performed on all rats prior to dosing and again before termination of the study (but see below).

Results: Presumably negative. No results were presented or described for this parameter in the study report.

5. Hematology: At termination of the study, all animals were fasted overnight (about 16 hours prior to blood collection). Each rat was then anesthetized with Ketamine HCl and about 5 ml of whole blood was withdrawn from the abdominal aorta. A 0.5 ml portion of the blood sample was mixed with EDTA anticoagulant for hematological investigations and the remainder was allowed to clot. The serum was separated by centrifugation. The following hematological determinations were made:

Erythrocyte count	Total WBC count
Hemoglobin concentration	Differential WBC count
Hematocrit	Platelet count

Results: None of the hematological parameters examined suggested a treatment related effect in males or females.

6. Clinical Chemistries: The clinical chemistries listed below were performed on samples of serum prepared from all animals at termination of the study (i.e. at 90 days).

Fasting glucose	Aspartate aminotransferase (SGOT)
Serum calcium	Urea nitrogen
Phosphorous	Albumin
Chloride	Blood creatinine
Sodium	Total and direct bilirubin
Potassium	Total serum protein
Alanine transferase (SGPT)	

Results: None of the clinical chemistry parameters examined suggested a treatment related effect in males or females.

7. Urinalyses: Urinalyses determinations were not conducted during the study.

8. Gross Necropsy: At termination of the study, all rats received a complete gross necropsy following collection of blood for hematology and clinical chemistry determinations.

Results: No effects attributable to the test material were observed during gross necropsy procedures. Mottled livers and mottled kidneys were frequently observed in both male and female rats in control and test groups, but were not considered to be treatment related because no histopathological effects were correlated with these observations.

9. Organ Weights and Relative Organ/Body Weight Ratios: The following organs were weighed and organ/body weight ratios calculated for each: liver, kidneys and testes.

Results: No biologically or toxicologically meaningful differences in organ weights or relative organ/body weight ratios were observed between male control and test groups or between female control and test groups.

10. Fixing of Tissues/Organs: Samples of (or the whole of) the following tissues/organs from each control and test animal were fixed in 10% neutral buffered formalin at the time of necropsy.

Normal and treated skin
All appropriate gross lesions
Brain (3 levels)
Pituitary
Thyroid/parathyroid
Thymus
Lungs
Heart
Aorta
Salivary gland (mandibular)
Liver
Spleen
Kidneys (2)
Adrenals (2)
Pancreas
Seminal vesicles (2)
Prostate
Epididymides (2)
Uterus
Oviducts and ovaries (2)
Cervix
Vagina
Esophagus
Stomach
Duodenum
Jejunum
Ileum
Cecum
Colon
Rectum
Urinary bladder
Lymph nodes (mesenteric, mediastinal)
Sciatic nerve
Trachea
Sternum
Mammary glands
Skeletal muscle
Femur
Spinal cord
Eyes

11. Histological Examination: All the tissues/organs listed above were examined by light microscopy for the sham control, vehicle control and high dose groups and for the one low dose female animal which was killed during week 11 (with a cranial mass and malignant lymphoma). A variable number (2-10) of additional slides of the liver, kidney and lungs from the male and female low and mid dose groups were also histologically

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examined. Tissues/organs were processed and slides prepared by the Histopathology Department, Health and Environmental Sciences, Dow Corning Corporation. Prepared slides were examined by Pathco Inc., Gaithersburg, Maryland.

Results: The low dose female which was killed during week 11 had a cranial mass and malignant lymphoma reported in several organs (e.g. liver, spleen, brain). This isolated neoplastic finding was not attributed to the test material. Acanthosis was consistently observed at the treated skin sites of nearly all animals treated either with the vehicle (propylene glycol) or with the test material (suspended in propylene glycol). The occurrence of this skin lesion was attributed to the propylene glycol vehicle, rather than to the test material per se. No other histopathological lesions were observed in any group which suggested a treatment related effect in males or females.

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Reviewed by: Irving Mauer, Ph.D., Geneticist
Toxicology Branch-I, HED (7509C)
Secondary Reviewer: Karl P. Baetcke, Ph.D., Chief
Toxicology Branch-I, HED (7509C)

9-29-94
9/30/94

DATA EVALUATION RECORD

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MRID No.: 413533-01 AND -02
PC No.: 107401
RD Record No.: [Not provided]
EPA ID No.: [Not provided]
Tox Chem. No.: [Not provided]
Project No.: D206465

I. SUMMARY

STUDY TYPE: (84-2) Mutagenicity---Gene mutation in mammalian cell cultures (L5178Y/TK)

CHEMICAL: DC 5700 hydrolysate [3- (trimethoxysilyl) propyl dimethyl octadecyl ammonium chlor]

SPONSOR: Dow Corning, Midland, MI

TESTING FACILITY: Hazleton Laboratories America (HLA), Kensington, MD

TITLE OF REPORTS: (1) Mutagenicity Test on DC 5700 Hydrolysate in the L5178Y TK+/- Mouse Lymphoma Forward Mutation Assay: Confirmation Study (MRID 41353301), and (2) Supplemental Studies to the Mutagenicity Test on DC 5700 Hydrolysate in the L5178Y TK+/-Mouse Lymphoma Forward Mutation Assay (MRID 41353302).

AUTHOR): Robert R. Young

STUDY NUMBER: HLA-10864-0-431

DATES ISSUED: December 26, 1989 (1), and January 02, 1990 (2).

EXECUTIVE SUMMARY: (MRID 41353301) In a single trial, mouse lymphoma (L5178Y) cells were exposed to test article up to levels of precipitation (62.5 ug/ml and higher) and/or cytotoxicity (6 ug/ml/-S9; 23 ug/ml/+S9) with no increase over control in mutant colonies (TK + to TK-).

TB-I EVALUATION:

(MRID 41353301) ACCEPTABLE

(MRID 41353302) [Not evaluated]

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II. DETAILED REVIEW

A. TEST MATERIAL: DC 5700 hydrosylate (Dow Corning)

Description: White powder
Batches (Lots): BN029263
Purity (%): [Not stated]
Solvent/carrier/diluent: Ethanol

B. TEST ORGANISM: Established mammalian cell strain

Species: Mouse lymphoma
Strain: L5178Y (TK +/TK-), Clone 3.7.2C
Source: Dr. D. Clive (Burrough-Wellcome, RTP, NC)

C. STUDY DESIGN (PROTOCOL): This study was designed to assess the mutagenic potential of the test article when administered in vitro to mouse lymphoma (L5178Y) heterozygous (TK +/TK-) cell cultures, and determining foreward mutation at the thymidine kinase locus (TK + to TK -), according to established (published) procedures and FIFRA Test Guidelines.

A Statement of Quality Assurance measures (inspections/audits) was provided.

A Statement of adherence to Good Laboratory Practice (GLP) was provided.

Report (1), MRID 41353301

D. PROCEDURES/METHODS OF ANALYSIS: Following preliminary dose-selection (cytotoxicity) testing, duplicate cultures (cleansed of spontaneous mutants[1]) were exposed for four hours to 7 or 8 dose levels of test article, in the absence or presence of a mammalian metabolic activation system, consisting of the commercially available S9 fraction of liver enzymes from a male S-D rat pre-treated with the hepatic PCB inducer of mixed function oxidase enzymes, Aroclor 1254, plus NADP(H)-generating co-factors. Treated cell cultures were then washed free of treatment medium, and allowed to recover for two days to allow development of mutants (expression period). Cultures were then cloned (split between a morning preparation and six hours later) and both transferred to medium continuing

[1] Customarily exposed for at least one day before use in tissue culture medium containing either aminopterin or methotrexate.

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trifluorothymidine (TFT, 3 ug/ml) for 10 to 14 days (selection phase), a treatment which permits only mutant (TK -/-) cells to survive, and grow into visible colonies.

The mutagens, ethylmethanesulfonate (EMS, 0.25/0.40 ul/ml) and 3-methylcholanthrene (MCA, 2.5/4.0 ug/ml) served as positive controls for, respectively, the non-activation and activation test series. Conventional criteria to affirm assay acceptance and response (evaluation of mutagenicity) were included in the Final Report.

E. RESULTS: [The data presented here for MRID 41353301 represents the last experiment, "Trial IV", of a series of trials, the first three of which manifested in what the investigators characterized as "conflicting results between independent trials both with and without metabolic activation"]

In preliminary range-finding testing (range: 1.95 to 1000 ug/ml), precipitation of test article was observed at concentrations of 62.5 ug/ml and higher, coincident with dose-related increases in cytotoxicity (reduction in cell growth) beginning at 3.91 ug/ml in non-activated (-S9) cultures and reaching near total lethality at 15.6 ug/ml, but only beginning at 7.81 ug/ml/+S9 and lethal at 62.5 ug/ml (Report Table 1).

Thus, the investigator selected 10 ug/ml as the HDT for the non-activation series and seven lower doses (to 0.5 ug/ml), but a HDT of 30 ug/ml under activation, accompanied by six lower doses (down to 0.5 ug/ml).

In the main non-activation assays, cytotoxicity (manifested as less than 10% relative-to-control suspension growth) was evident at the highest dosages (6, 7, 8 and 10 ug/ml), but mutant frequencies (total mutant colonies/total viable colonies times 2 X 10^6) varied randomly with dose and toxicity at both cloning times, but did not exceed at any dose twice the solvent control (Report Tables 2, 3 --- attached).

Under S9-activation, the HDT (30 ug/ml) cultures had to be terminated due to excessive toxicity, and the next lower doses (26, 23 ug/ml) had less than 10% relative growth, and were considered too toxic to evaluate (Report Tables 4, 5 --- attached). Nonetheless, none of the remaining cultures had mutant frequencies significantly increased over solvent controls, as defined by less than background threshold values (169.1 and 180.3 X 10^{-6}).

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In both types of assay, positive control values were greatly in excess of background, 8 - 10 X control for EMS, and 5 - 8 X control for MCA. Thus, the author concluded that the test article was negative (non-mutagenic) in the mouse lymphoma foreward mutation assay under both activation and non-activation conditions.

F. TB EVALUATION: [MRID 41353301] ACCEPTABLE

[MRID 41353302] [Not evaluated, but see ADDENDUM (next page)].

ATTACHMENTS: Data Tables (MRID 41353301]

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ADDENDUM.

Report (2), MRID 41353302, represents a report of supplemental studies attempting to explain the reason for the anomalous results obtained with DC 5700 Hydrosylate in an initial set of experiments performed early in 1989[2]1, in which "...one trial had an abnormally high number of surviving colonies in mutant selection plates that increased with a dose-related pattern... (i.e., appeared definitively positive for compound-induced mutation), "...while independently repeated assays showed no effect on mutant frequency." (i.e., essentially negative).

In a series of asssays conducted to identify procedural variables which could have impacted trifluorothymidine selection to produce these claimed "false-positive" results, the investigator discovered (and documented in the data tables presented in this supplementary report) that the presumed anomalous results in the first trials were a procedural artifact of " .... physiological effects of test material treatment combined with variations in the heat-inactivation process that resulted in a weakening of the selective pressure."

[2] Young, R: "Mutagenicity Test on DC 5700 Hydrosylate in the L5178Y TK +/- Mouse Lymphoma Foreward Mutation Assay" (Hazleton Laboratories America, 34 pp) --- not submitted to this reviewer (IM) for review and evaluation.

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