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Test: Lifetime Feeding Study in Rats

EPA Acc. No. 241208

Test Initiated: December 30, 1976

MRID 00079877

Test Terminated: January 2 and 5, 1979

Report Submitted to Sponsor: October 1979

Report Lab. No. LBI Project No. 20733-01

Facility: Litton Bionetics Inc.
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0006
(1)

Title: Lifetime Feeding Study in Rats.
SD-43775 Technical.

Purpose:

The purpose of this study was to further evaluate and characterize the chronic toxicity of SD-43775 at a previously untested high dose level. This study is to complement an earlier two year rat chronic toxicity study [LBI Project No. 20541; Toxicology Branch Reference Caswell #77A; PP 7F2013; Acc. No. 097075-097082; see Review by Dr. Larry Anderson July 17, 1978 LBI Proj. No. 2541 (Sic ?)]

Materials and Methods:

Twenty-one-day old outbred albino rats [CRL: COBS CD (SD) Br; Charles River Breeding Laboratories, Wilmington, Massachusettes] were acclimated for nine days, prior to dosing, to the laboratory conditions in the Falls Church, Virginia facility of Litton Bionetics. The animal rooms were within the clean-dirty barrier system. The annual room temperature ranged between 71 and 77° F, and a 12 hour light-dark cycle was maintained. There were no other compounds on test in the rooms used for this study, other than a separate and concurrent study (LBI Project No 20733-02) in SD-43775. The test diet was prepared by dissolving 10 grams of 98% pure technical SD-43775 in acetone to make a 25 ml. solution and then blending this solution with standard Purina Laboratory Chow meal (5001) for each 10 kg of feed prepared. [Initially from December 30, 1976 to January 26, 1977 the solvent in the diet preparation was hexane. The change reflected the concern of possible peripheral nerve effects due to use of hexane.] The mix was achieved by first blending the solvent/test material solution with a mortar and pestle into a few hundred grams of the basal diet and then adding this premix to a Patterson-Kelly twin shell blender equiped with an intensifier bar, which contained approximately one-half the final volume of feed. After blending for 15 minutes, the remaining half of the feed was added and the mixture was blended again for another 15-20 minutes. This procedure resulted in a blend of 1000 ppm.

The control diet was prepared by mixing 10-15 ml of solvent into the chow meal for each kilogram of diet.

The control and experimental diets were analyzed five times between November 10, 1977 and October 25, 1979, for the presence and concentration of SD-43775. All the analytical results were within 10% of the nominal concentration.

The standard Purina Chow meal (50C1) diet was also periodically analyzed for the presence of cholrinated pesticides, aflatoxins, metals and antibiotics.

The heat treated, hardwood chip bedding (AB-SORB-DRI) was alos periodfcally analyzed for polychlorinated biphenyls and pentachlorophenol.

Tap water, prior to acidification, was sampled on August 15. 1978 for conformance with EPA's interim drinking water standards. The purpose of acidifiying the tap water is to keep the level of Psuedomonas spp (bacterial organisms commonly found in tap water) low.

The results of the analysis for bedding, feed and water are appended to this review

Twenty-one day old outbred albino rats [CRL: COBS CD (SD) BR; Charles River Breeding Laboratories] were divided into two groups of 50 animals per sex per group. The experimental group received 1000 ppm of SD 43775 in the diet whereas the controls were treated similarly but had the test chemical excluded from their feed. The animals were initially housed for a one month period three per cage in suspended polycarbonate cages with AB-SORB-DRI bedding and later two per cage. The relative position of the cages on the rack remained constant until week forty-one (41) of the study. After week 41 the rows of cages were moved approximately monthly in a regular sequence (i.e. top row to the bottom, second row from the top to the top row, etc.). All animals received bottled acidified (ph 2.5) tap water and their respective diets ad libitum. The animals were observed daily for mortality or a moribund condition for the first year and a half of the study and thereafter twice daily. Body weight for each individual animal was taken once every four weeks. Food intake data were collected once every four weeks on twenty percent of the animals (first five cages of each group) Once every four weeks the animals were examined clinically and palpated for masses.

Animals dying intercurrently (found dead) or judged to be moribund and killed were necropsied. Surviving animals were killed at termination of the study (January 2, 1979 through January 5, 1979) One day prior to necropsy, the animals were fasted and urine was collected overnight with the use of stainless steel metabolism cages. The parameters evaluated were:

Color
Appearance
Specific gravity
pH
Protein (presence of albumin)
Glucose
Ketones
Bilirubin
Occult blood
Microscopic examination of sediment

After urine samples were collected, blocd was collected by use of the orbital sinus bleeding technique for the following clinical chemistry (serum) determinations:

Bilirubin
Urea Nitrogen
Albumin
Chloride
Cholesterol
Creatine phosphokinase
Creatinine
Serum glutamic-oxaloacetic transaminase
Alkaline phosphatase
Phosphorus
Total protein
Globulin
Albumin/globulin ratio
Potassium
Sodium
Uric acid
Calcium
Glucose

After sufficient blood was obtained for the clinical chemistry analyses, the animals were administered uthol (pentobarbital, sodium, 5 g/cc). As soon as each rat lost consciousness, the animal was opened and sufficient blood was collected from the aorta for the following hematologic tests:

Red blood cell count
White blood cell count
Differential leukocyte count
Hematocrit
Platelet count (adequacy)
Sedimentation rate
Prothrombin time
Hemoglobin
Clotting time

Following blood withdrawal for the hematology tests, the animals were necropsied by pathology prosectors under the supervision of William Hall, V.M.D., Veterinary Pathologist. During the necropsy, organ weights were taken on the following organs:

Brain
Heart
Liver
Testes
Spleen
Adrenal glands
Kidneys

Suitable samples of the following organ/tissues from the animals killed terminally, as well as those dying intercurrently, were preserved in 10% neutral formalin, and were then trimmed, processed and microslides prepared at 4-6 microns. Tissue sections were primarily stained with hematoxylin and eosin. However, selected sections of sciatic nerve were stained with luxol fast blue for myelin and sections of subcutaneous spindle cell sarcomas were stained to demonstrate collagen, reticulum, and mucin. The following tissues were examined by William Hall, D.V.M.:

Brain	Small intestine (three sections)
Pituitary gland	Large intestine
Eyes, if abnormal	Adrenal gland
Salivary gland, submaxillary	Kidneys
Thyroid gland	Lymph nodes (mesenteric)
Parathyroid gland (when present in plane of section)	Bladder
	Prostate gland
Larynx	Testes/ovaries
Trachea	Uterus
Esophagus	Fallopian tubes
Thymus	Skin (back)
Mammary gland	Skeletal muscle (thigh)
Heart	Bone with marrow (femur)
Lungs	Spinal cord
Liver	Peripheral nerve (sciatic)
Spleen	Pancreas
Stomach	Nasal cavity

The statistics for the various parameters measured, as appropriate, were compared using the Dunnett's t-test or Chi-square test. Values differing from the control values were considered significant when $p < 0.05$.

Results:

Cumulative Mortality and Early Female Deaths: The percent cumulative mortalities for controls of both sexes as well as treated males were similar. Treated females showed a slightly higher cumulative mortality, than either males or controls. However, females were not statistically different from control females and generally appeared to be within the range of cumulative mortality for all groups. The treated females did however die somewhat earlier than the other groups, but the rate of death appeared to be similar for all groups. The total number of deaths at termination of the study is shown below by category of death.

Dose Level (ppm)	Sex	Found Dead	Moribund Killed	Subtotal Found dead/ Moribund	Terminal Kill	Total
Control	Male	13	10	23	27	50
Control	Female	3	18	21	29	50
1000	Male	8	13	21	30	51*
1000	Female	7	17	24	25	49*

* One animal mis-sexed.

An inspection of the graphs representing percent cumulative mortality with respect to time for both males and females indicates the initial period for the uniform rate of death was as noted below:

	Beginning Period for Uniform Death Rate	
Dose	Male	Female
0	64 weeks	86 weeks
1000 ppm	80 weeks	70 weeks

It can be seen that females receiving compound began dying approximately 16 weeks earlier than their own controls and 10 weeks earlier than males receiving test compound. Males receiving 1000 ppm began dying later than their controls only because their own controls started dying relatively early. However, had male controls lived longer (as one would normally expect) or as long as female controls, then the males on test compound would have started dying approximately the same time as their own controls

Body weight: Males showed a consistent decrease in body weight which was statistically significant from week 16 thru 104. Males therefore sustained a 64 week time period of lowered body weight before they began dying with any regularity (week 80 when animals began dying with regularity minus week 16, time period of statistically significant weight decrease). Females showed a consistent decrease in body weight which was statistically significant from week 44 thru to week 104. Females therefore sustained a 26 week period of decreased body weight before they started dying with any regularity (i.e. 70-44 weeks = 26 weeks).

Females, therefore, began losing weight later than males but began dying off earlier, and males began losing weight sooner than females but began dying later than females.

It would therefore appear that males although affected earlier were better able to tolerate (thru various possible appropriate mechanisms) the chemical, whereas females while able to tolerate the chemical in the early stages of its administration succumed earlier once the tolerance mechamism was overwhelmed.

However, to reiterate, both sexes began dying off at a uniform rate once the mechanism(s) for handling the xenobiotic were dissipated.

Daily Food Intake: The daily food intake between test and control animals was comparable with no significant differences noted for males during the duration of the experiment. There was also no statistically significant difference between females and their own respective controls. Therefore, the weight lost by the test animals can not be attributed to decrease feed consumption.

Tissue Massses: Tissue masses were described as small, medium and large. Papillomas were also included in the category "tissue masses" but were described separately. However, the total number of masses reported included all palpable masses and were not necessarily tumors. Included in the category of masses were such biological manifestations as active mammary tissue, scar tissue formed by cutaneous lesions, masses due to salivary gland infection, and local infections.

The number of male and female animals receiving test compound, and showing at least one mass, was not significantly different from their own controls. The total number of masses (including multiple masses per animal) between males on test and control males were comparable.

The total number of masses including multiple masses per animal between females on test and control females indicated that control females had 1.5 times more masses than the females receiving the test compound.

Therefore, an arguement can be made that the early deaths in the females, which was noted earlier in this review, were in part caused by compound administration and not solely to the presence of the size, number and type of masses. The size, number and type of masses in females did not appear to be treatment related in females (or males).

Hindlimb Weakness: Six male rats receiving compound showed hindlimb weakness within eight weeks of the initiation of the experiment. Hindlimb weakness was not seen in females. This weakness was characterized by an abnormal gait. The rear legs would appear to falter, and the rat would compensate for this weakness by using its front legs to pull itself along the floor of the cage. It was judged by the authors of the report that this condition was related to administration of the test material.

The male animals coded 7185, 7186, 7197, 7198 manifested hindlimb weakness during the third week of observation. Hindlimb weakness was not observed at week four or during any later period for these four animals. The effect can be considered transient and reversible. Two of these animals were sacrificed at the terminal kill and two were found dead at 105 weeks.

Animals numbered 7194 and 7203 manifested hindlimb weakness at the fourth week of observation. Both animals survived the experiment to the terminal kill. Animal 7194 showed no signs of hindlimb weakness before or after week four, however, the animal numbered 7203 showed evidence of hindlimb weakness at week eight, but not at the next observation period which was week 12. The onset and duration of signs were difficult to estimate due to the time intervals of the observation periods.

The examination of other parameters including histopathology for each of the above animals gave no readily acceptable cause for the hindlimb weakness nor any readily available hypothesis for the observed effect. Additionally, hair loss for each of the above animals did not appear to correlate with hindlimb weakness.

Hair Loss: Male and female animals both control and test animals (all dose levels) were compared for hair loss by this reviewer. The time periods arbitrarily chosen by this reviewer were 26, 50 and 98 weeks.

Male control rats showed no hair loss at the arbitrary selection period of 26 weeks. Only one male control rat showed some hair loss at 50 weeks (animal #7121) behind the right ear. Only one animal (#7128) showed some slight hair loss behind the left ear. All these animals survived to the period of the terminal kill.

Seven males on test at 26 weeks showed some hair loss. Five of the animals survived the duration of the experiment. At 50 weeks eight animals showed some hair loss and seven of these survived the experimental duration. Five animals showed some hair loss at 98 weeks and all five were sacrificed at the time of terminal kill.

Three of five animals showing hair loss at 98 weeks were also the same three animals that showed hair loss at 26 and 50 weeks. Animals numbered 7214, 7226 and 7229 generally showed a relatively stable alopecia at the three time periods. Some of the animals in this arbitrary sample that showed hair loss at either 26 or 50 weeks did not show hair loss at succeeding time periods. Furthermore, hair loss was almost always confined to the upper part of the body of these animals.

It is also noted that of all the test animals recorded as showing hair loss in this arbitrary sample, only three died inter-currently.

It is the opinion of this Toxicology Branch reviewer that for males fed 1000 ppm of test compound, for this arbitrary selection of time periods it appears that for this sample:

1. Hair loss is not correlated with death of the animal.

2. Hair loss is apparently not time dependent in that the number of animals showing alopecia does not increase with time, and that the severity of the alopecia does not appear to increase with time.

3. Hair loss in some instances was reversible.

Control females and female rats receiving the test compound, when examined for weeks 26, 50 and 98, generally showed quantitative and qualitatively similar responses. The conclusions arrived at for males are therefore also applicable here for females. In those instances of recorded generalized hair loss (98 weeks), the hair loss was usually accompanied by some sort of large tissue mass.

Generally speaking for both male and female test animals as most of the alopecia was confined to the upper body, one might speculate that at least in some cases, hair loss may be due to animals fighting, or some other non-compound related cause. Age as related to alopecia should also not be ruled out in some cases.

Hematology: Males. Reported values for males receiving the test compound were comparable to controls. Females showed comparable values between those receiving the test compound and those not receiving the test compound for all categories of measurement except two; hemoglobin and packed cell volume were significantly lower than control values. It is however difficult to accept these results at face value for the following reasons - packed cell volume is essentially a function of the formed elements of the blood. The results of the measurements of individual formed elements showed comparable values between test and control animals. Therefore, as the individual formed elements of the blood are comparable to controls, packed cell volume should also be comparable between animals receiving test compound and their own controls. The lower hemoglobin value in test animals is not affirmed by the ancillary data within the report. The test animals were not reported as suffering

from dyspnea. Pathology and organ weight data did not indicate cardiac compensation as manifested by an enlarged heart. The red blood cell count was normal as were bilirubin levels. The histopathological examination of bone with marrow was also reported as normal. Additionally, review of the data does appear to support a conclusion for hemodilution.

Therefore, based upon the report it would appear that the lowered values for packed cell volume and hemoglobin might be attributed to some other cause rather than to the administration of the test compound.

Clinical Chemistry: Serum-glutamate-oxalate - transaminase levels, in females were statistically significantly decreased when compared to control values. However, as one would normally expect an increase in these levels as a manifestation of a toxic effect the reported values are therefore not considered by this reviewer as being biologically meaningful, and most likely are not a result of compound administration.

The significantly increased glucose levels in male rats may or may not be compound related. Sodium levels were statistically significantly lower in females, whereas, potasium was statistically significantly elevated in males. The results for both these alkali metals may be artifact (chloride values were comparable for test and controls) or related to the compound's effect upon the kidney. However, other possibilities may exist for glucose, sodium and potassium when considered together, such as adrenal and/or pitiutary gland involvement.

Urinalysis: Inspection of each of the parameters measured did not reveal a compound-related effect when the test groups were compared to their respective controls.

Protein Electrophoresis: Protein electrophoresis was conducted on serum protein and numerical values were determined for total protein, albumin, alpha-1-globulin, alpha-2-globulin, beta globulin, gamma globulin and the albumin-globulin ratio. Male rats showed no significant differences between treated and control animals for the values recorded. Female, showed no significant differences between values from treated and controls with the exception of a statistically significant increase in gamma globulin values for treated groups (8.69% for controls vs. 12.24 for treated). However, there does not appear to be a readily available explanation for these results from the data available. Parenthetically, however, viral or bacterial invasion should not be ruled out, as a possible explanation, nor the compound itself which may act as an antigen, and therefore stimulate the antibodies. Experimental error should also not be ruled out.

Organ Weight: The actual (absolute) organ weights of the treated animals were similar to controls. The organ weight - body weight percentages (i.e. ratio) however were significantly higher in males for the brain, liver, heart, spleen and testes and in females for the brain, kidneys, liver, spleen and heart. This increase was due to the lowered body weight of treated animals when compared to controls. The increased organ weight - body weight percentages were therefore judged to be related to treatment with the test material, but of no toxicologic significance.

Pathology: The final pathology report made mention of the fact that interstitial cell testicular tumors were found in 5 of 50 male rats receiving the test compound but only 1 of 50 control animals manifested this tumor. The author of the report further stated that although the incidence of this lesion was low in the control group of this study, interstitial cell tumors were found in 5 of 80 Sprague-Dawley rats used as controls of a similar age and reared at Litton Bionetics, from a separate and previously conducted study (see summary pages of final pathology report pp. 00280-00284; Accession No. 241208). It was then concluded that the lesions were not compound related.

This Toxicology Branch reviewer does not agree with the rational for the conclusion presented by the author for these two reasons: (1) it should be noted that even though the incidence in these connective tissue type tumors are numerically low, no evidence was presented as to their statistical significance or non-significance. The level of significance or non-significance should have been established and the statistical method referenced, and (2) if a matching control group is available historical controls can not be used. The rationale presented by the sponsor would obviate the need for concurrent controls and eventually lead to a host of problems of interpretation of data submitted in future studies.

This Toxicology Branch reviewer does however agree with the conclusion of the author in that the interstitial cell tumors are probably not compound related. It is generally known that interstitial cell tumors are common in aging rats. One aging rat of the control group was found to have an interstitial tumor, at the time of the terminal kill. The terminal kill occurred at about 24 months after the initial compound administration and coincided with the ending of the normal life-span of the rat. Five rats of the treated group were found to have interstitial cell tumors. Three of the rats had interstitial cell tumors as diagnosed at the time of terminal kill. Two of the five rats which showed interstitial cell tumors died intercurrently. However, these two animals, 7199 and 7213,

died on November 21 and August 11 of 1978. The terminal kill took place between January 2 and January 5, 1979. Therefore these two rats were by ordinary standards old rats. Interstitial cell tumors were not found in other males dying intercurrently. Therefore, interstitial cell tumors do not appear to be compound related based upon what is generally known and the results of this experiment. Additionally, Bert Litt, the Toxicology Branch statistician provided a statistical analysis of the one tumor found in the controls versus the five tumors found in the treated group, using the Fisher's Exact Test. Mr. Litt's conclusion was that the incidence in the treated group was borderline as to its statistical significance, with a "p" value equal to or less than 0.0913.

Therefore it is the belief of this Toxicology Branch reviewer that the interstitial tumors in male rats are probably not compound related because the tumors are (1) not uncommon in aging male rats and (2) the statistical significance is borderline as judged by Mr. Litt.

The author of the report also concluded that the spindle cell sarcomas that were observed in the subcutis and dermis of 5 out of 51 treated males (9.8%) but not in the concurrent (matched) controls (zero out of 50) only suggested compound relatedness.

Animals Showing Spinale Cell Sarcomas

Terminal Kill	Animal No.	Time
January 5, 1979	7224	24 months
January 5, 1979	7230	24 months
Moribund Kill	**Animal No.**	**Time**
October 18, 1978	7188	22 months
August 11, 1978	7213	20 months
Natural Death	**Animal No.**	**Time**
November 23, 1977	7227	11 months

The author stated that the historical data from the Archies at Litton Bionetics and information from the literature indicated that the spindle cell sarcomas were observed more frequently in control male rats of Other reported studies in animals of this strain and age than were observed in the controls of this reported study. In those other studies (refer to pp. 00282 of Accession No. 241208) the incidence of such lesions ranged from zero to 6%, thus indicating a possibility of the chance occurrence of spindle cell sarcomas in test animals of this study. The author of the pathology report concluded that the results of this single dose study were equivocal but not clearly negative.

This Toxicology Branch reviewer disagrees with the conclusion in this section of the report for the following three reasons: (1) historical controls can not be used if matched concurrent controls are available (please refer to this reviewer's opinion on the use of historical controls which appears earlier in this discussion), (2) it is noted that even though the incidence of these connective tissue type tumors was five no evidence was presented as to their statistical significance, and (3) a statistical analysis using the Fisher's Exact Method was conducted by Mr. Bert Litt, the Toxicology Branch Statistician, using data as reported for spindle cell sarcomas. The Toxicology Branch statistician, Mr. Bert Litt concluded that the tumor incidence was significant at a "p" value equal to or less than 0.027 (see attached).

It is therefore concluded by this reviewer that the test chemical SD43775 and/or one or more of its metabolites is the apparent causative agent of spindle cell sarcomas under the conditions of the experiment and available evidence but is apparently not related to the incidence of interstitial cell tumors which are probably related to the natural aging of the animals.

Sparately the pathology report also stated that the neoplasms of the anterior pituitary gland were the most frequently occurring tumor of the study. Anterior pituitary tumors were observed in 59% of the male controls and in 59% of males receiving the test compound. Anterior pituitary tumors were also found in 67% of the control females and 67% of the females receiving the test compound. These percentage values are correct as reported. This reviewer conducted an individual count of all animals and noted which individual animals manifested anterior pituitary gland tumors. The results of this survey are noted below:

Anterior Pituitary Tumors

Males:	Control	Test
	28/48 = 58.3%	30/51 = 58.8%
Females:	Control	Test
	33/49 = 67.3%	33/48 = 68.7%

The numerator indicates the number of animals identified by the pathologist as having anterior pituitary tumors.

The denominator indicates the total number of animals (i.e. tissue) examined.

It is also interesting to note here that of the five male rats which manifested interstitial cell tumors, only two of these animals (#7199 and 7219) had anterior pituitary tumors. The three remaining animals (#7214, 7213 and 7214) which manifested interstitial cell tumors did not show any apparent evidence for a pituitary tumor even though interstitial cell tumors were diagnosable.

Conclusion:

It is therefore concluded that:

(1) SD 43775 produces spindle cell sarcomas in male rats as defined by the experimental conditions.

(2) SD 43775 elicits a statistically significant body weight decrease in males and females at the singular dose tested, 1000 ppm.

(3) SD 43775 is the apparent cause of hindlimb weakness in male rats (6/50) which is transient, reversible, and apparently without long-term aftrer effects.

(4) Interstitial cell tumors are not, in the opinion of this reviewer, compound related.

Classification: Core-Guideline

OPP:HED:TOX: A.KOCIALSKI:sb 12/17/80 X77395 TS-769 Rm. 820 CM 2 #8

Synopsis of effects at 1000 ppm - only dose tested.

- Survival rate for males and females was 50-60% at the end of two years.
- Females receiving the test compound began dying 10 weeks earlier than males receiving the test compound.
- Males from week 16 and females from week 44 showed statistically significant and consistent weight loss for the duration of the experiment.
- Daily food intake was comparable for all groups.
- Tissue masses was a generic term encompassing all kinds of masses.
- Reversible hindlimb weakness was evident only in some males, within 12 weeks of compound administration. The effect was compound related.
- Hair loss did not appear to be compound related.
- Hematology for all groups was comparable.
- Urinalysis for all groups was comparable.
- Clinical chemistry - values for SGOT glucose, Na and K differed from controls but no definitive conclusions were made as to their significance.
- General protein electrophoresis indicated a raised gamma globulin value for females, but the relationship to the compound is uncertain.
- Organ weights were comparable for all groups.
- Spindle cell sarcomas were statistically significant in males and compound related.
- Interstitial cell tumors were evident in males but not compound related.

Questions:

1. Please provide the Agency with a rational for the selection of the particular strain of rat [CRL: COBS CD (SD) Br] utilized in this study.

2. Please provide the Agency with a rationale for the selection of the dose level used in this study.

3. The protocol states that the animals were observed daily for mortality and/or a moribund condition during the first year of the study and once every four weeks the animals were examined clinically. Please provide any other data, previously considered not pertinent (if such circumstances existed), regarding the onset, description, severity and duration of the animal sign "hindlimb weakness", in the animals observed in this study. This Toxicology Branch reviewer finds it quite surprising and remiss on the part of the sponsor and contractor that this effect was not given the due attention it deserved.

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Page_____ is not included in this copy.

Pages 17 through 18 are not included.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

X FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Fisher's Exact Test

To Allen Kocialski.

Re Fyden (SD 43775); Fenvelurate Sunicidin (S-5602; #24377)

	Treated	Control	All	Exact Test
⇨ Spindle Cell Sarcomas	5	0	5	$\frac{5!\,50!\,51!\,96!}{54!\,46!\,50!\,101!} = .026566$
⇨ Fac of above	46	50	96	
# Examined	51	50	101	

The Probability of 5 Sarcomas or fewer in 51 Treated animals compared with zero of 50 Controls .026566 as a result of chance alone, ie $P = .027$

	Treated	Control	All	
Interstitial Cell Tumors ⇨	5	1	6	
⇨ Fac of above	45	49	94	$\frac{6!\,50!\,50!\,94!}{5!\,45!\,50!\,100!} + \frac{6!\,44!\,50!\,94!}{6!\,44!\,50!\,100!} =$
# Examined	50	51	101	$.03837 + .052746216 = .09133$

The probability of observing 5 cases of Interstitial Cell Tumors in 50 rats treated with compound #1 of 50 Controls is .0913 as a result of chance alone, ie $P = .0913$

This finding is a statistically significant finding ($P = .026$) of more Spindle cell sarcomas in male rats treated with compound #1 and borderline finding of increased frequency of interstitial cell tumors ($P = .0913$) in male rats.

11/3/80

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Addendum:

This Toxicology Branch reviewer includes the following comments with regard to the author's use of historical data. It is included as an aside from the official review but not necessarily excluded from the review itself.

The author uses the phrase... "Sprague-Dawley rats of similar origin".... This statement is to some extent true in that all Sprague-Dawley rats had a common origin. However, there are probably several breeders (suppliers) of Sprague-Dawley rats, each with its own currently evolved line of genotype. Although all the lines may be relatively similar, genetic variation exists between the lines thereby dictating a possible range of responses between genetic lines (pharmacogenetics). The direct comparison of responses between different genetic lines of the same strain separate by time, space and experimental protocol would therefore not appear to be appropriate. The author's statement can therefore be considered vague and some what misleading. The impression given is that similar lines are identical (i.e. no genetic difference between lines) and therefore one can expect an identical response between genetically evolved lines. This is not necessarily true.

The author also refers to several previous studies conducted at Litton Bionetics, the National Cancer Institute and the open publised literature for support of his position that the spindle cell sarcomas are not uncommon in this strain of rat and, that the incidence in the test sample is comparable to those of previous historical controls. The author stated that the incidence of spindle cell sarcomas ranged between zero and six percent. If one lists the frequency (f) of spindle cell sarcomas for the five referenced studies conducted at Litton Bionetics, Inc. (LBI) one obtains the following:

Reference		"f"	Percent
LBI	Project No. 20541	2/102	2%
LBI	Project No. 20823	2/50	4%
LBI	Project No. 20876	0/50	0%
LBI	Project No. 20584	0/64	0%
LBI	Project No. 1400	0/83	0%

The range of responses for spindle cell sarcomas is from 0 to 4% for these individual studies. This is one way of examining the data. However, noting what has previously been stated in the earlier paragraphs, it would appear that a better representation of the population incidence for spindle cell sarcomas could be obtained by summing up the individual incidences and the population size for each experiment. If one looks at the data in this manner then the frequency of response would be 4/349 which is equal to about 1.14%.

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If one totals up the incidences of spindle cell sarcomas for the four literature references one obtains the following:

Reference	"f"	Percent
MacKenzie and Garner, 1973	4/535	0.74
Thompson et al , 1969	1/16	6.20
N. C. I. Bioassay	1/215	0.50
N. C. I. Bioassay	1/25	4.00

If one adds up the total incidences for the four references the incidence becomes 7/791 equivalent to 1.0%.

A total of all the incidences for all the historical referenced data (present study excluded) reveals a ratio of 11/1140 for a percentage incidence of 1.0%.

It would therefore appear that as the population sample gets larger the natural incidence becomes smaller (i.e. it tends towards a 1.0% incidence or less) and therefore the test group (i.e. males receiving SD 43775 at 1000 ppm in this reported experiment) having an incidence of 5/51 equivalent to 9.8%, compared to zero incidence for concurrent controls appears significanly increased from the aggragate population as a whole. The caveat however is that we are probably comparing different genetic lines of the same strain and therefore some room for error may exist, but still in all, by adding up all the individual population groups the differences between the various groups may well have been greatly diminished and in turn would support the Toxicology Branch position that the incidence of 5/51 spindle cell sarcomas, 9.8% of the sample size, is both biologically and statistically meaningful.

If we are not comparing different lines of the same strain, but the same genetic lines of the same strain (i.e. animals not separated by time, space, and experimental protocol), then the data proposed by the author of the pathology report would also appear to support the position of this Toxicology Branch reviewer.

It is also known that the results of acuce studies (Weil and Scala - reference not known) between laboratories for the same chemical compound vary greatly. If one extends the concept of the variability of results between laboratories for acute studies to chronic studies, then the number and magnitude of the variables and the variable animal responses can easily be evisioned.

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

009003

CAS. No. 77A

April 3, 1981

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE:

SUBJECT: (1) Toxicologic and Carcinogenic Study of SD-43775 by Dietary Administration to Mice for Two Years. (2) A Lifetime Dietary Feeding Study in Rats of SD-43775 at the Singular Dose Level of 1000 ppm.

FROM: Albin B. Kocialski, Ph.D.
Toxicology Branch/HED (TS-769)

TO: F. D. R. Gee, PM #17
Registration Division (TS-769)

THRU: Robert Coberly
Decision Unit Leader
Toxicology Branch/HED (TS-769)

Petitioner: Shell Oil (Chemical) Company
Suite 200
1025 Connecticut Ave., N.W.
Washington, D.C. 20036

Recommendation: It is requested that the Shell Chemical Company respond to the reviewer's questions appearing at the end of each summary and conclusion of the oncogenic studies.

Conclusions: Dietary administration of Pydrin (SD-43775) at 1000 ppm results in the production of spindle cell sarcomas in male rats of the [CRL: COBS CD (SD) Br] strain.

Dietary administration of Pydrin (SD-43775) at 1250 ppm results in no observable oncogenic effects in mice of the 86C3F1 strain.

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(17)

addendum 83-5, 2 rat. Fenvalerate

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

009004

009004

MEMORANDUM

DATE: JUL 21 1981

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Retraction of the Conclusion in My Previous Memorandum Stating that Pydrin® When Fed to Male Rats of the [CRL: COBS CD (SD) Br] Strain at 1000 ppm for a Period of Two Years Resulted in the Manifestation of Spindle Cell Sarcomas in the Subcutis Under the Conditions of the Test.

TOX Chem. No. 77A

FROM: Albin B. Kocialski, Ph.D. ABK
Section II, Toxicology Branch/HED (TS-769)

TO: F. D. R. Gee, PM #17
Registration Division (TS-767)

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch/HED (TS-769)

Rec'd 7/10/81 Hfn 6273

This memorandum is issued as a retraction of my original conclusion that the administration of Pydrin® resulted in the manifestation of spindle cell sarcomas in male rats. This reversal of opinion is based upon the review of additional and more detailed information (previously not available) submitted by the Shell Chemical Company on June 15, 1981.

The original conclusion arrived at by this reviewer was based on the original data as it was presented. The Shell Chemical Company, when informed of the Agency's conclusion, did the following: (1) three board-certified veterinary pathologists on the Shell staff independently re-examined the original pathology slides and compared Dr. Hall's (contract pathologist) conclusions against their own findings and (2) they also resectioned and examined several of the tissues in question. A ten page addendum to the original study entitled "Addendum: Lifetime Feeding Study in Rats SD-43775 Technical LBI Project No. 20733-01" (attachment No. 1) was then submitted by the company contending that the five subcutaneous tumors in test males previously termed spindle cell sarcomas, actually represented at least three separate tumor types that were related only in their embryonal origin. Additionally, it was pointed out that three (or possibly four) of the fifty male control rats also showed malignant mesenchymal tumors or sarcomata one of which was a true spindle cell sarcoma. The Shell Chemical Company therefore concluded that what originally appeared to be a tumorogenic effect was in reality a spurious effect resulting from an unconventional tumor classification and assimilation.

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The submitted ten page addendum was reviewed by the Toxicology Branch pathologist Dr. Louis Kasza. Dr. Kasza concluded (attachment No. 2) that the detailed description of the five malignant tumors in the high dose male group was sufficient to justify the new classification of these tumors. Furthermore, Dr. Kasza concluded that these neoplasms in the high dose male group were similar and comparable to three neoplasms in the control group.

This reviewer now concludes that the nearly equal incidences of sarcomata in the control male rats (3 or 4 out of 50) and the high dose male rats (5 out of 51) precludes the original interpretation of a generalized sarcomagenic effect.

The original conclusion is therefore retracted.

This memorandum also makes unnecessary any previously contemplated exposure and/or risk assessment for this chemical with regard to this issue.

Attachment

cc: Christine F. Chaisson
Caswell File No. 77A

OPP:HED:TOX: A.KOCIALSKI:sb 7/8/81 X77395 Rm. 824 CM 2 #1

PYDRIN

Page_____ is not included in this copy.

Pages 25 through 34 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

X FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

009004

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460
June 26, 1981

OFFICE OF TOXIC SUBSTANCES

MEMORANDUM

TO: Albin Kocialsky, Ph.D.
Toxicology Branch, TS-769

FROM: Louis Kasza, D.V.M., Ph.D. L.K
Toxicology Branch, TS-769

SUBJECT: Pathologic Evaluation of Addendum, Shell Pydrin Report

In the Addendum, the detailed description of the five malignant tumors in the high dose group justified the new classification of the five sarcomas. Also the detailed description of the three malignant tumors in the control group indicates that the diagnosed neoplasms in the high dose group (5 sarcomas) and in the control group (3 sarcomas) are comparable.

In the evaluation of the significance of the incidence of sarcomas in the high dose group, the above-mentioned findings should be considered.

10-1-79

DER #3

Fenvalerate: 2-Year Feeding Study in Rats
Shell Chemical Company. 1979. MRID No. 00079877. HED Doc. No. 009003.