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TOXICITY STUDIES ON OIL ADDITIVES:

ONE GENERATION REPRODUCTION STUD. IN

MALE RABBITS REPEATEDLY TREATED

DERMALLY WITH SAP 011 FOR 18 WEEKS

COVER LETTER 050484

Chemical Name (300 per name)	25	CAS No. (10)	24
NAPHTHENATE CALCIUM		61789-36-4	

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Shell Oil Company

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TRDB

May 4, 1984

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EPA INFO. CONTROL

Mr. Phillip Wirdzek
Test Rules Development Branch (TS-778)
U. S. Environmental Protection Agency
Waterside Mall
401 M Street, S.W.
Washington, D.C. 20460

Dear Mr. Wirdzek:

As indicated in my letter of December 20, 1983, concerning calcium naphthenate, Shell Oil Company is submitting the following:

1. Group Research Report - SBGR.83.335
   Toxicity Studies on Oil Additives: One Generation Reproduction Study in Male Rabbits Repeatedly Treated Dermally with SAP 011 for 10 Weeks

2. External Report - SBER.84.002
   Toxicity Studies on Oil Additives: One Generation Reproduction Study in Male Rabbits Repeatedly Treated Dermally with SAP 011 for 10 Weeks

The External Report (No. 2) is a "sanitized" copy of the Group Research Report in which confidential business information has been deleted. As such, it is appropriate for release if deemed necessary. The Group Research Report is for EPA use only and is considered confidential.

If EPA disagrees with any part or all of Shell's deletion of confidential business information, please contact us before releasing any material other than the enclosed "sanitized" copy of the report.

If you have any questions, please contact me at (713) 241-0070.

Very truly yours,

J P Sepesi

J. P. Sepesi, Manager
Product Safety & Compliance
Oil & Chemical Products, HS&E

JPS/cjm

Attachments

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40-8471080

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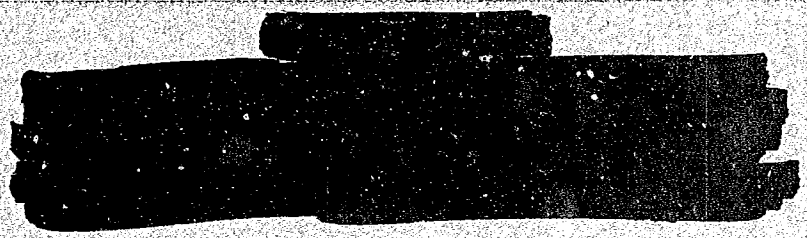
EXTERNAL REPORT

SBER.84.002

TOXICITY STUDIES ON OIL ADDITIVES: ONE GENERATION REPRODUCTION STUDY IN MALE RABBITS REPEATEDLY TREATFD DERMALLY WITH SAP 011 FOR 10 WEEKS

COMPANY SANITIZED

SICC, CSASA Budget Ref: 500 70 639



SHELL RESEARCH LIMITED, LONDON

SITTINGBOURNE RESEARCH CENTRE

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DOCUMENT TYPE: EXTERNAL REPORT

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TITLE: TOXICITY STUDIES ON OIL ADDITIVES: ONE GENERATION REPRODUCTION STUDY IN MALE RABBITS REPEATEDLY TREATED DERMALLY WITH SAP 011 FOR 10 WEEKS.

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PROJECT NUMBER: SRCSAR83

SUB PROJECT: 2624

PROJECT TITLE: Toxicity of Additives.

SPONSOR: SICC, CSASA

BUDGET CODE: 500 70 639

SOURCE: Shell Research Limited, Sittingbourne Research Centre

ORIGINATING DIV: Toxicology and Pathology Division

DATE: September, 1983

[redacted] TOXICITY STUDIES ON OIL ADDITIVES: ONE GENERATION REPRODUCTION STUDY IN MALE RABBITS REPEATEDLY TREATED DERMALLY WITH SAP 011 FOR 10 WEEKS.

(EXPERIMENT NUMBER 2624)

SUMMARY:

Work done

A group of 12 proven male New Zealand White rabbits was dermally exposed to 2 ml undiluted SAP 011 for 6 hours daily for 5 days each week over 10 weeks. A control group of 12 male rabbits was similarly exposed to the carrier oil present in SAP 011.

Bodyweights were recorded weekly and at the end of 10 weeks each male was mated with 2 untreated female New Zealand White rabbits. Half of the males of each group were killed and necropsied after mating. The remaining males were weighed weekly and necropsied approximately 12 weeks later. Macroscopic and microscopic examinations of the male reproductive tracts were carried out on all rabbits.

The females were necropsied on day 29 of gestation. Numbers of corpora lutea, total implantations, pre- and post-implantation losses and numbers of viable foetuses were recorded.

Results

1. All male rabbits survived with the exception of one control that died after 9 weeks of exposure, having shown no unusual clinical signs.

2. There were no adverse signs of toxicity either systemically or at the site of application in the SAP 011 treated males or the controls during the exposure or post exposure periods.

3. There were no statistically significant differences in bodyweights between the control and the SAP 011 treated males during the 10 week exposure period or the 12 week post-exposure period. Testes weights of SAP 011 treated males killed after mating or 12 weeks later did not differ significantly from their respective controls.

4. No statistically significant differences were observed between the numbers of SAP 011 treated males and their controls achieving at least one viable litter, two viable litters or two pregnancies in their females.

5. Numbers of implantations, pre- and post-implantation losses and viable foetuses were not significantly different for the litters of unexposed females mated with SAP 011 exposed males compared with those of controls.

6. There were no macroscopic or microscopic pathological findings of the male reproductive tract that could be related to SAP 011 exposure.

7. It is concluded that repeated dermal exposure of male rabbits to SAP 011 over a period of ten weeks did not adversely affect their reproductive capacity.

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Date: January 1984

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CONTENTS

		Page No.
STUDY INFORMATION		5
PERSONNEL		6
INTRODUCTION		7
EXPERIMENTAL PROCEDURES		8
RESULTS		12
DISCUSSION AND CONCLUSIONS		15
REFERENCES		16
TABLES		
1. A + B Bodyweights of males		17 & 18
2. A + B Testes weights of males		19 & 20
3. Fertility data of male rabbits		21
4. Litter data of untreated females mated with treated males		22
5. A + B Summary of macroscopic findings		23 & 24
6. A + B Summary of microscopic findings		25 - 31
APPENDIX 1	Compound Control and Formulation Chemistry Report	32 - 35
APPENDICES 2A & B	Individual bodyweights of male rabbits	36 - 41
APPENDICES 3A & B	Individual testes weights of exposed male rabbits	42 - 47
APPENDIX 4	Mating allocation of untreated females to treated males	48
APPENDIX 5	Individual litter data of the untreated females mated to the treated males	49
APPENDICES 6A & B	Individual macroscopic and microscopic findings of the male rabbits	50 - 61
APPENDIX 7	Individual macroscopic findings of the non-pregnant female rabbits	62
QUALITY ASSURANCE STATEMENT		63

STUDY INFORMATION

Testing facility:	Sittingbourne Research Centre, Biotechnology and Toxicology Directorate, Sittingbourne, Kent, ME9 8AG, England.
Dates:	Protocol approved 9th February 1983.
Archives:	All specimens, raw data and the final report are stored in Sittingbourne Research Centre (Shell Research Ltd.), under Experiment SAR 2624.

[redacted]

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INTRODUCTION

SAP 011 is an oil additive, comprising overbased calcium naphthenate in mineral oil which is subsequently referred to as carrier oil.

This study investigated the reproductive performance of male rabbits exposed dermally to SAP 011 during a spermatogenic cycle. The dermal route of exposure was chosen, as this is likely to be the most common route of human exposure. The rabbit was used as the test species since it is suitable for dermal toxicity testing. In order to carry out exposure over the duration of a complete spermatogenic cycle, the rabbits were treated repeatedly over a 10 week period. This was followed by evaluation of male breeding performance and pathological changes of the male reproductive tract.

Preliminary studies were carried out to determine the maximum tolerated exposure of SAP 011, applied repeatedly under an occlusive dressing, which would prevent ingestion of the chemical and also maximise absorption. Repeated exposures of 2 or 3 ml undiluted SAP 011 caused slight skin irritation at the application site, which declined over 3 weeks only in the 2 ml group. No apparent stress was observed in the rabbits exposed to 2 ml SAP 011 and this was chosen as the exposure volume for the main study. The carrier oil, was similarly tested in the preliminary study as a control and 2 ml exposure volumes were also found to be suitable for use in the main study.

EXPERIMENTAL PROCEDURES

Test substance (Appendix 1)

The sample of SAP Oil used, in this study, was supplied by Shell Chemicals U.K. Ltd., Stanlow and was considered to be stable for the duration of the study. The negative control substance was the carrier oil as present in the SAP Oil ; this was also received from Shell Chemicals U.K. at Stanlow.

Both materials were used undiluted.

Animals

New Zealand white rabbits bred in the Shell Toxicology Laboratory (Tunstall) rabbit breeding unit were used. The males were proven before commencement of the study and were approximately 6 to 9 months of age. The females were virgins, aged between 5 and 8 months at the time of mating. They were individually numbered by means of ear tags. They were housed singly throughout the study in stainless steel cages with mesh floors and tops and half mesh fronts. Sawdust-filled trays were placed under the cages and were cleaned twice weekly. Water and food (Standard Rabbit Diet SQC, Special Diet Services Ltd., Witham, Essex) were available ad libitum throughout the study. During the experiment, the animals were housed in two rooms in the Rabbit Experimental Unit. The temperature was maintained between 15 and 25°C, lying in the range 17-19°C for most of the time. The relative humidity varied between 36 and 77% but was predominantly in the range 50-60%. Lighting (fluorescent tube) was on an automatic 12 hour cycle (0600-1800 hours on, 1800-0600 hours off).

Methods

Dermal exposure phase

On Friday February 11th, 1983, twenty four proven male rabbits were weighed and allocated by the statistician to treatment groups, on the basis of litter information and bodyweight as shown below.

		No. of males
Group 1	2 ml carrier oil (control)	12
Group 2	2 ml SAP Oil	12

On Sunday February 13th, 1983, they were shaved in the upper scapular region over an area approximately 10 x 10 cm. Shaving was carried out thereafter, throughout the study on Sundays and Wednesday afternoons (post exposure). On Monday, February 14th, and each weekday (Monday-Friday)

thereafter for 10 weeks (last day of exposure Friday, 22nd April), each rabbit was dermally exposed on the shaved area via a 7 x 7 cm piece of lint BP on which 2 ml of the test material had been placed, followed by immediate application of an occlusive dressing (10 x 10 cm polythene kept in place by 3M Blenderm) for 6 hours. At the end of the 6 hours, the occlusive dressing was removed and the application site was washed with warm, weak Nonidet P40 (Shell Chemicals U.K. Ltd.) solution, to remove unabsorbed material, followed by thorough rinsing with warm tap water and drying. Daily clinical observations (including application site) were made throughout the study and body weights were recorded each Friday.

Reproductive phase

The females were weighed prior to mating. The females' bodyweights were used in the allocation of the females to the males, ensuring that lighter and heavier females were evenly distributed between the two treatment groups. Female siblings were not mated with the same male and males were not mated with their female siblings. Each male mated (day 0) two females, so that they had two opportunities in which to establish their fertility, thus making some allowances for any failure to conceive due to the virgin females. One female was mated on Monday 25th April and the other on Tuesday 26th April (STL SOP 151). After mating each female was injected intravenously with 25 i.u. luteinising hormone (Chorulon, supplied by Intervet of Bar Hill, Cambridge) to ensure ovulation. Each mated female was singly housed and given hay as nesting material on day 22. Daily clinical observations were made of each female. On day 29 of gestation, Tuesday May 24th or Wednesday May 25th, all females were necropsied, following intravenous injection of pentobarbitone sodium. The ovaries were fixed in 10% neutral formalin prior to the counting of corpora lutea. The uteri were opened and the numbers of resorption sites, live and dead foetuses were recorded for each female (ST SOP 116). The foetuses were killed by subcutaneous pentobarbitone sodium injection and discarded. No tissues, with the exception of the ovaries, were retained. The presence of any macroscopic pathological lesions was recorded for non-pregnant females. On Wednesday April 27th, half the male rabbits in the control and SAP 011 group were randomly chosen and were killed and necropsied. The remaining male rabbits were weighed weekly for 12 weeks. When all data, including the results of pathological examinations of the first half of the male rabbits, had been assessed and further matings were considered to be unnecessary, the remaining males were killed on 20th and 21st July, 1983.

Pathological procedures of the male rabbits

The rabbits were weighed and then killed by intravenous pentobarbitone sodium. Viscera and treated skin were examined grossly and the presence of any macroscopic lesions was recorded. Both testes of each rabbit were removed, examined and weighed (STL SOP 92). They were fixed in Bouin's fluid in 500 ml plastic pots (ST SOP 102). The ductuli efferentes, caput and cauda epididymides, vasa deferentia and caudal epididymal ligaments were examined and placed intact on a piece of wood and immersed in Bouin's fluid in the same pot as the testes. After 24 hours, these tissues were removed and placed in 70% alcohol. Blocks of the above tissues were trimmed and processed for haematoxylin and eosin-stained paraffin sections, following standard histological procedures (ST SOP 91, 159, 197 and 198). In addition to the above procedures, small samples of ductuli efferentes

from 3 controls and 3 treated rabbits, necropsied on 20.7.83, were placed in Regaud's fluid (3% K_2CrO_4 in 10% formalin fixative), immediately after necrospy, as an aid to microscopic identification of ectopic adrenal/embryonic tissue (Chromaffin Cell Reaction, CFA Culling, 1974).

The male rabbit that died prior to the scheduled necropsy date was subjected to the same procedures as surviving rabbits with the exception of organ weight recording.

All sections were examined microscopically and the findings were recorded for each male rabbit. Testicular changes were examined in detail. Seminiferous tubules were considered to be atrophic if they were shrunken and contained degenerate germinal epithelium with few, if any, developing germ cells. Tubules of normal size which showed a reduced population of cells undergoing spermiogenesis and spermatogenesis were classified as hypoactive. The percentages of atrophic or hypoactive tubular cross-sections and those cross-sections showing pyknotic spermatid nuclei, single or multiple degenerate spermatocytes, multinucleate spermatids or sloughing of the epithelium were estimated for each pair of testes. Detailed microscopic findings of the ductuli efferentes, epididymides and vasa deferentia were also recorded.

Statistical methods

Male rabbits were allocated to blocks of four so that any rabbits from the same litter were placed in the same block. The males were then randomly allocated to the two treatment groups so that each treatment group was represented twice in each block and the mean bodyweights of the two treatment groups were similar.

When testing for statistically significant differences between control and treated groups, two sided tests were used throughout. Any significant differences at either 0.05 or 0.01 probability levels were reported.

Bodyweights

For weeks 1-10, bodyweights of male rabbits were analysed using a two way analysis of covariance, the factors being treatment and block. Bodyweight at week 0 was included as a covariate for weeks 1 to 10 inclusive and also for weeks 11-22 inclusive, for males retained after mating. A one way analysis of covariance taking bodyweight at week 0 as a covariate was used for the data for weeks 11-22. A two way analysis was not possible because in one of the blocks there were data for only one animal.

The significance of the difference between treated and control group means was tested using Students 't' test.

Testes weights

For the week 10 data, the significance of the covariance relationship between testes weights and initial and terminal bodyweights was tested,

but not found to be significant so a two way analysis of variance was used, the factors being treatment and block. For testes weights at week 22 a one way analysis of variance was used since the relationship of testes weight with either initial or terminal bodyweight was not significant. A two way analysis of variance was not possible because in one of the blocks there were data for only one animal.

The significance of the difference between treated and control group means was tested using Student's 't' test.

Litter data

The significance of any difference between control and treated groups for corpora lutea, total implantations, live foetuses and pre- and post-implantation losses was tested using Wilcoxon's two sample rank test with ties (Pearson and Hartley (1972), Hill and Peto (1971)). The male was taken as the experimental unit (i.e. the mean value of the females mated to each male was analysed). When the two matings of a male rabbit resulted in only 1 litter, the data of the single litter were used in the analysis.

Fertility data

The significance of any difference in variates relating to male fertility (i.e. number of males mating two females that became pregnant, number of males mating at least one female that had viable foetuses and number of males mating two females that had viable foetuses) was tested using Fisher's exact test (Fisher 1954).

RESULTS

Clinical observations and mortality

No signs of systemic toxicity or local toxicity at the site of application were observed in either control or SAP 011 treated males. One control male (number 391) died after 9 weeks of treatment; no adverse clinical signs were seen in this animal prior to death.

No unusual clinical signs were observed during pregnancy in the unexposed females mated with either control or SAP 011 treated males, with the exception of reduced food intakes in 3 females (559 and 560 mated with control males, 549 mated with a SAP 011 treated male) during the latter half of pregnancy. All females survived to day 29 of gestation.

Bodyweights (Tables 1 A and B, Appendices 2A and B)

There were no significant differences in bodyweights between the control and the SAP 011 treated groups of male rabbits either during the exposure period or during the 12 weeks after mating.

Testes weights (Tables 2 A and B, Appendices 3A and B)

There were no significant differences in testes weights between the control and the SAP 011 treated group, for either the males killed after mating or the males killed 12 weeks later.

Male fertility (Table 3, Appendices 4 and 5)

All males readily mated the two females presented to them, except one control male (511) which was rejected by his second female. She was replaced by a spare female rabbit.

There were no statistically significant inter-group differences in the number of males achieving at least one viable litter, two viable litters or two pregnancies. All males successfully impregnated at least one female at the end of the 10 week exposure period, with the exception of one SAP 011 treated male (258) which impregnated neither of the females he mated. Total litter loss, due to both pre- and post-implantation losses occurred in one of two pregnancies produced by control male 383.

Litter data of unexposed females mated to exposed males (Table 4, Appendices 4 and 5)

No significant differences between the control and the SAP 011 treated group were found for the numbers of corpora lutea, total implantations, live foetuses or pre- and post-implantation losses.

Pathological findings

Macroscopic pathology (Tables 5A and B, Appendices 6A and 7)

Males

All rabbits killed, either at the end of 10 weeks dermal exposure or 12 weeks later, were in good general condition. A low incidence of minor background findings were observed, none of which was in the reproductive tract. It was noted that 3 of the carrier oil (control) exposed rabbits killed 12 weeks after the end of exposure had poor hair growth at the site of treatment although the skin was healthy.

The control rabbit (391) that died 9 weeks after commencement of dermal exposure, without any prior adverse clinical signs, was found to be in good condition at necropsy. Focal haemorrhages on the thymus, and haemorrhagic lungs with froth and blood clots in the trachea were observed. The exact cause of death was not determined.

Females

All females were observed to be in good condition at necropsy. The lesions observed in the reproductive tract in 3 of the 8 non-pregnant females (small unilateral paraovarian cyst, small unilateral fallopian tubal cyst or the presence of cloudy fluid in the vaginal/cervical region, respectively) were not considered to be associated with non-pregnancy.

Microscopic pathology of male rabbits (Tables 6A and B, Appendix 6B)

Low incidences of minor background changes (usually below 3% of tubular cross-sections) were observed in the testes of all rabbits. These comprised atrophied or hypoactive seminiferous tubules, pyknotic spermatid nuclei, single or multiple degenerate spermatocytes, multinucleate spermatids, rare degenerate spermatogonia, sloughing of the epithelium or intertubular fluid accumulation. There were no differences in the incidences of these findings, between control and treated males of groups killed after mating and those killed 12 weeks later, that were of any toxicological significance.

The mild inflammatory and round cell infiltration of the ductuli efferentes, observed in small numbers of both treated and control rabbits killed after mating, was not observed in those rabbits killed 12 weeks later. Minor epithelial cell changes, sometimes with inflammatory cell infiltration in the caput epididymides and more rarely in the cauda

epididymides, were observed in both treated and controls. Varying degrees of inflammatory cell infiltration of the caudal epididymal ligament was present in most rabbits. All these minor changes were considered to be background findings in the male rabbits and unrelated to SAP 011 exposure. The incidences or degree of these changes observed in rabbits killed 12 weeks after the end of exposure did not differ from those of rabbits killed after mating. No differences were observed between treated and control rabbits in the germ cell populations present in the lumina of the ductuli efferentes, epididymides or vasa deferentia.

DISCUSSION AND CONCLUSIONS

The objective of this study was to investigate the reproductive performance of male rabbits, exposed dermally to SAP 011 during the period of a spermatogenic cycle.

Exposure to SAP 011 was not accompanied by any manifestations of stress; no changes occurred at the site of application to the skin, in body weights or in general health and behaviour.

The reproductive performance of rabbits exposed to SAP 011 was not affected. Litter data of the females mated with the treated males showed no significant differences from those of females mated with controls. There were no differences in testes weights and no gross or microscopic treatment-related findings in the male reproductive tract. All 11 surviving control males and 11 of the 12 SAP 011 exposed males produced at least one viable litter showing them to be fertile. The SAP 011 treated male which failed to achieve pregnancy in its two females showed no adverse pathological findings in the reproductive tract that could account for this failure. Non pregnancy of some females of this study is likely to be the result of inexperience of the rabbits used, as the females were virgins and the males had not had the opportunity to mate since the proving mating, four months prior to this study.

It is concluded that repeated dermal exposure of male rabbits to SAP 011 over the duration of the spermatogenic cycle did not adversely affect their reproductive capacity.

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Table 1A - Mean bodyweights of male rabbits over the 10 week treatment period

	Treatments		
	Control	SAP 011	SD of a single observation
No. of rabbits	12	12	
Week 0 grams	3848.5	3782.7	417.59
Week 1 grams +	3778.3	3791.7	55.32
Week 2 grams +	3821.6	3843.0	60.74
Week 3 grams +	3820.7	3835.8	68.06
Week 4 grams +	3897.3	3897.3	79.40
Week 5 grams +	3923.5	3920.3	95.21
Week 6 grams +	3905.2	3916.1	122.12
Week 7 grams +	3949.6	3945.9	109.82
Week 8 grams +	3941.9	3948.2	150.56
Week 9 grams +	3986.2	3947.1	164.52
Week 10 grams +	3986.4^{-1}	3937.5	151.08

No significant differences between control and treated means using Student's 't' test.

+: values adjusted for initial bodyweight (BWT000)

Superscript (-1) indicates the missing value for male 391 which died after 9 weeks exposure.

Table 1B - Mean bodyweights of male rabbits over the 12 week post-treatment period

	Treatments		
	Control	SAP 011	SD of a single observation
No. of rabbits	6	6	
Week 0 grams	3603.2^{-1}	3909.7	302.95
Week 11 grams +	3959.9^{-1}	3863.1	285.54
Week 12 grams +	3960.6^{-1}	3899.2	252.71
Week 13 grams +	3966.7^{-1}	3878.8	222.46
Week 14 grams +	3990.1^{-1}	3907.6	249.33
Week 15 grams +	3983.9^{-1}	3927.8	271.33
Week 16 grams +	4019.7^{-1}	3900.6	278.15
Week 17 grams +	4045.7^{-1}	3908.9	277.93
Week 18 grams +	4056.8^{-1}	3923.3	278.33
Week 19 grams +	4062.3^{-1}	3928.4	285.00
Week 20 grams +	4053.2^{-1}	4016.7	225.43
Week 21 grams +	4059.7^{-1}	4008.5	211.69
Week 22 grams +	4071.4^{-1}	4013.5	206.62

No significant differences between control and treated means using Student's 't' test.

+: values adjusted for initial bodyweight (BWT000) of the 6 animals in each group.

Superscript $^{(-1)}$ indicates the missing value for male 391 which died after 9 weeks exposure.

Table 2A - Mean testes weights of male rabbits killed immediately post exposure

	Treatments		
	Control	SAP 011	SD of a single observation
No. of rabbits	6	6	
Mean initial body weight (g)	3968.0	3655.7	385.78
Mean testes weights (g)	6.00	5.92	0.608

No significant differences between control and treated groups using Student's 't' test.

Table 2B - Mean testes weights of male rabbits killed 12 weeks post exposure

	Treatments		
	Control	SAP 011	SD of a single observation
No. of rabbits	6	6	
Mean initial body weight (g)	3603.2[-1]	3909.7	302.95
Mean testes weights (g)	5.75[-1]	5.53	0.906

No significant differences between control and treated means using Student's 't' test.

Superscript [-1] indicates the missing value for male 391 which died after 9 weeks exposure.

Table 3 - Fertility data of male rabbits mated immediately after the 10 week exposure period

	Treatments	
	Control	SAF 011
No. of males mated	11	12
No. of males that mated at least one female that produced viable foetuses	11	11
No. of males that mated two females that produced viable foetuses	9	6
No. of males that mated two females that became pregnant	10	6

No significant differences between control and treated group using Fishers exact test.

Table 4 - Mean litter data of untreated females mated with treated male rabbits

	Treatments	
	Control	SAP 011+
No. of males mated	11	12
	Mean values	
Corpora lutea	11.7	11.2
Total implants	8.1	8.3
Live foetuses	7.2	7.7
Resorptions	0.7	0.5
Dead foetuses	0.1	0.1
Pre-implantation losses	3.6	2.9
Post-implantation losses	0.9	0.6

+ The data of this group are based on the results of matings of 11 males only as Male 258 produced no pregnancies in his two females.

No significant differences between control and treated group using Wilcoxon's two sample rank sum test.

When the 2 matings of a male resulted in only 1 litter, the data of the single litter were used.

Table 5a - Summary of macroscopic findings in male rabbits killed after 10 weeks dermal exposure to carrier oil (control) or SAP 011

Findings	Dermal exposure (2 ml/day)	Control	SAP 011
	Group size No. of rabbits	6	6
Good general/external condition		6 (100)	6 (100)
Depressed lesions on internal surface of aortic arch		3 (50)	1 (17)
Necrotic lesion on skin (not exposure site)		1 (17)	0 (0)
Lungs: slightly patchy appearance		0 (0)	1 (17)

( ) = percentages of rabbits affected.

Table 5B - Summary of macroscopic findings in male rabbits killed 12 weeks after the end of dermal exposure to carrier oil (control) or SAP 011

Findings	Dermal exposure (2 ml/day)	Control	SAP 011
	Group size No. of rabbits	5*	6
Good general/external condition		5 (100)	6 (100)
Poor hair growth on neck/interscapular region where dermal exposure took place		3 (60)	0 (0)
White depression on internal surface of aortic arch		1 (20)	2 (33)
Small right kidney with renal pelvis containing calculi; large left kidney		1 (20)	0 (0)

( ) = percentages of rabbits affected

* An additional rabbit from this group (M 391) that died 9 weeks after commencement of dermal exposure showed the following:

External/general condition:	Normal
Stomach and intestines:	Normal contents
Lungs:	Dark, haemorrhagic appearance (all lobes)
Trachea:	Contains some froth and blood clot
Thymus:	Focal haemorrhages

Table 6A - Summary of microscopic findings in rabbits killed after 10 weeks of dermal exposure to carrier oil (control) or SAP 011

Findings	Dermal exposure (2 ml/day)	Control	SAP 011
	Group size	6	6
	No. of rabbits with/without lesions (%)		
Testes			
Percentages of atrophic tubules			
	<1%	3 (50)	2 (33)
	1-3%	1 (17)	1 (17)
No atrophic tubules		2 (33)	3 (50)
Percentages of hypoactive tubules			
	<1%	4 (67)	4 (67)
	1-3%	2 (33)	2 (33)
	4-6%	0 (0)	0 (0)
No hypoactive tubules		0 (0)	0 (0)
Percentages of tubules showing pyknotic spermatid nuclei			
	<1%	6 (100)	5 (83)
	1-3%	0 (0)	1 (17)
No pyknotic spermatid nuclei		0 (0)	0 (0)
Percentages of tubules showing single degenerative spermatocytes			
	<1%	6 (100)	6 (100)
Percentages of tubules showing multiple degenerate spermatocytes			
	<1%	5 (83)	4 (67)
	1-3%	0 (0)	1 (17)
No multiple degenerate spermatocytes		1 (17)	1 (17)

(Contd.)

Table 6A - Contd.

Findings	Dermal exposure (2 ml/day)	Control	SAP 011
	Group size	6	6
	No. of rabbits with/without lesions (%)		
Percentage of tubules showing multinucleate spermatids			
	<1%	3 (50)	3 (50)
	1-3%	3 (50)	2 (33)
	4-6%	0 (0)	1 (17)
No multinucleate spermatids		0 (0)	0 (0)
Percentages of tubules showing sloughing of the epithelium			
	<1%	2 (33)	1 (17)
No sloughing of epithelium		4 (67)	5 (83)
Inter-tubular fluid accumulation			
	mild	5 (83)	6 (100)
	moderate	1 (17)	0 (0)
No inter-tubular fluid		0 (0)	0 (0)
Rare degenerate spermatogonia		0 (0)	0 (0)
Ductuli efferentes			
Small foci necrotic epithelial cells		0 (0)	1 (17)
Mild focal interstitial lymphocytic infiltration		3 (50)	0 (0)
Mild focal inflammatory cell infiltration		1 (17)	2 (33)
Spermatids/spermatocytes/multinucleate spermatids:small numbers		5 (83)	4 (67)
spermatids:moderate numbers		1 (17)	2 (33)
Adjacent ectopic adrenal/embryonic tissue		1 (17)	2 (33)
Caput epididymides			
Rare degenerate/necrotic/pyknotic epithelial cells occasionally with inflammatory cells		5 (83)	3 (50)
Inter-tubular inflammatory cell focus		1 (17)	1 (17)

Contd.

Table 6A - Contd.

Findings	Dermal exposure (2 ml/day)	Control	SAP 011
	Group size	6	6
	No. of rabbits with/without lesions (%)		
Caput epididymides (contd.)			
Small intra epithelial cysts		2 (33)	3 (50)
Mild intra epithelial brown secretion		2 (33)	3 (50)
Moderate intra epithlial brown secretion		1 (17)	0 (0)
One mineralised tubule seen		0 (0)	0 (0)
Fine cytoplasmic vacuolation of epithelium		1 (17)	0 (0)
Occasional mitoses		5 (83)	6 (100)
Occasional spermatids		2 (33)	3 (50)
Moderate spermatids/spermatocytes		4 (67)	3 (50)
Occasional multinucleate spermatids		4 (67)	3 (50)
Moderate multinucleate spermatids		2 (33)	2 (33)
Normal spermatozoa present in lumen		6 (100)	6 (100)
Cauda epididymides			
Spermatids/spermatocytes: mild		4 (67)	4 (67)
Spermatids/spermatocytes: moderate		2 (33)	1 (17)
Multinucleate spermatids: mild		3 (50)	2 (33)
Multinucleate spermatids: moderate		1 (17)	2 (33)
Normal spermatozoa present in lumen		6 (100)	6 (100)
Rare tubule showing pyknotic nuclei		1 (17)	0 (0)
Focal cytoplasmic vacuolation of epithelium		1 (17)	0 (0)
Caudal epididymal ligaments			
No. of rabbits in which 1 of the 2 ligaments was not microscopically examined		2 (33)	1 (17)
Inflammatory cell infiltration of one or both ligaments: mild		0 (0)	2 (33)
Inflammatory cell infiltration of one or both ligaments: moderate		2 (33)	1 (17)
Inflammatory cell infiltration of one or both ligaments: marked		1 (17)	1 (17)
Inflammatory cell infiltration of one moderate + 1 mild		0 (0)	1 (17)
Small round cell aggregates		1 (17)	0 (0)
Vasa deferentia			
Rare or occasional spermatids		4 (67)	1 (17)

Table 6B - Summary of microscopic findings in rabbits killed approx. 12 weeks after end of dermal exposure to carrier oil (control) or SAP 011

Tissue and lesion	Dermal exposure (2 ml/day)	Control	SAP 011
	Group size	5*	6
	No. of rabbits with/without lesions (%)		
Testes			
Percentages of atrophic tubules			
	<1%	4 (80)	3 (50)
	1-3%	1 (20)	1 (17)
No atrophic tubules		0 (0)	2 (33)
Percentages of hypoactive tubules			
	<1%	1 (20)	2 (33)
	1-3%	4 (80)	2 (33)
	4-6%	0 (0)	2 (33)
No hypoactive tubules		0 (0)	0 (0)
Percentages of tubules showing pyknotic spermatid nuclei			
	<1%	4 (80)	6 (100)
	1-3%	0 (0)	0 (0)
No pyknotic spermatid nuclei		1 (20)	0 (0)
Percentages of tubules showing single degenerate spermatocytes			
	<1%	5 (100)	6 (100)
No single degenerate spermatocytes		0 (0)	0 (0)
Percentages of tubules showing multiple degenerate spermatocytes			
	<1%	4 (80)	4 (67)
	1-3%	0 (0)	0 (0)
No multiple degenerate spermatocytes		1 (20)	2 (33)
Percentages of tubules showing multinucleate spermatids			
	<1%	5 (100)	5 (83)
	1-3%	0 (0)	1 (17)
	4-6%	0 (0)	0 (0)
No multinucleate spermatids		0 (0)	0 (0)

* Microscopic findings for rabbit 391 at end of Table 6B.

Contd.

Table 6B - Contd.

Tissue and lesion	Dermal exposure (2 ml/day)	Control	SAP 011
	Group size	5*	6
	No. of rabbits with/without lesions (%)		
Percentages of tubules showing sloughing of the epithelium			
	<1%	2 (40)	3 (50)
No sloughing of epithelium		3 (60)	3 (50)
Inter-tubular fluid accumulation: mild		4 (80)	6 (100)
Inter-tubular fluid accumulation: moderate		0 (0)	0 (0)
No inter-tubular fluid		1 (20)	0 (0)
Rare degenerate spermatogonia		2 (40)	3 (50)
Ductuli efferentes+			
Small foci necrotic epithelial cells		0 (0)	0 (0)
Mild focal interstitial lymphocytic infiltration		0 (0)	0 (0)
Mild focal inflammatory cell infiltration		0 (0)	0 (0)
Spermatids/spermatocytes/multinucleate spermatids: small numbers		4 (80)	6 (100)
	moderate numbers	1 (20)	0 (0)
Adjacent adrenal/embryonic tissue		1 (20)	2 (33)
Caput epididymides			
Rare degenerate/necrotic/pyknotic epithelial cells occasionally with inflammatory cells		3 (60)	4 (67)
Intertubular inflammatory cell focus		0 (0)	0 (0)
Small intra epithelial cysts		5 (100)	4 (67)
Mild intra epithelial brown secretion		3 (60)	3 (50)
Moderate intra epithelial brown secretion		0 (0)	1 (17)
One mineralised tubule seen		1 (20)	0 (0)
Fine cytoplasmic vacuolation of epithelium		0 (0)	1 (17)

+ The additional pieces of tissue taken from this region from M 495, 527, 529, 516, 386 and 504 and fixed in dichromate formalin did not contain adrenal/embryonic tissue

* Microscopic findings for rabbit 391 at end of Table 6B.

Contd.

Table 6B - Contd.

Tissue and lesion	Dermal exposure (2 ml/day)	Control	SAP 011
	Group size	5*	6
	No. of rabbits with/without lesions (%)		
Caput epididymides (contd.)			
Occasional mitoses		3 (60)	4 (67)
Occasional spermatids		5 (100)	5 (83)
Moderate spermatids/spermatocytes		0 (0)	0 (0)
Occasional multinucleate spermatids		0 (0)	3 (50)
Moderate multinucleate spermatids		0 (0)	0 (0)
Normal spermatozoa present in lumen		5 (100)	6 (100)
Cauda epididymides			
Spermatids/spermatocytes: mild/rare		5 (100)	5 (83)
Spermatids/spermatocytes: moderate		0 (0)	0 (0)
Multinucleate spermatids: mild/rare		2 (40)	3 (50)
Multinucleate spermatids: moderate		0 (0)	0 (0)
Normal spermatozoa in lumen		5 (100)	6 (100)
Rare tubule showing pyknotic epithelium nuclei		0 (0)	0 (0)
Focal cytoplasmic vacuolation of epithelium		0 (0)	1 (17)
Caudal epididymal ligaments			
Number of rabbits in which 1 of the 2 ligaments was not microscopically examined		0 (0)	1 (17)
Inflammatory cell infiltration : mild		3 (60)	1 (17)
Inflammatory cell infiltration: moderate		0 (0)	4 (67)
Inflammatory cell infiltration: marked		0 (0)	0 (0)
Small round cell aggregate		3 (60)	0 (0)
Vasa deferentia			
Rare or occasional spermatids		2 (40)	2 (33)

* Male rabbit 391 that died 9 weeks after commencement of dermal exposure had the following findings:

Testes (partly autolysed)		
Percentage of atrophic tubules	<1%	
Percentage of tubules containing pyknotic spermatid nuclei	<1%	

See over page for remainder of findings

Percentage of tubules showing single degenerate spermatocytes	<1%
Percentage of tubules showing multiple degenerate spermatocytes	<1%
Percentage of tubules showing multinucleate spermatids	<1%

Ductuli efferentes - no lesions

Caput epididymides - (partly autolysed)

Spermatids - occasional
Multinucleate spermatids - occasional
Spermatozoa - present

Cauda epididymides - (partly autolysed)

Spermatozoa - present

Caudal epididymal ligament - mild inflammatory cell infiltration in left ligament

Vasa deferentia - no lesions

Thymus - congested

Lungs - congested

[redacted] SBER.84.002

Title of Main Report: One generation reproduction study in male rabbits repeatedly treated dermally with SAP 011 for 10 weeks.

Experiment Number: 2624

APPENDIX 1

Title of Appendix: Compound Control and Formulation Chemistry Report.

Summary: Data describing the test and control substances and their formulations are reported.

Participant: M. D. Crowne

Responsible Practitioner: _____ (Signature) 20th January 1984 (date)

Data checked by: M.K Bond (Signature) 20th January 1984 (date)

Scientific Reviewer: M K Bond (Signature) 20th January 1984 (date)

1. TEST SUBSTANCE

1.1 Identity of the test substance

The data for the test substance released for use in this experiment are tabulated below.

NAME	SAP 011
BATCH NUMBER	3046/46, (Ref. 699519)
ST NUMBER	ST83/002
SOURCE	Shell Chemicals U.K. Ltd., Stanlow
DATE RECEIVED AT STL	11 January 1983
APPEARANCE	Dark brown viscous oil
COMPOSITION	Overbased calcium naphthenate in approx. 53% carrier oil. Further details were supplied to STL on a CONFIDENTIAL basis.
DENSITY	1.078 g/ml @ 20°C
DATE RELEASED	10 February 1983

1.2 Storage of this test substance

Following its arrival in STL this test substance was stored in the dark at ambient temperature under nitrogen.

1.3 Stability of this test substance

The test substance data sheet supplied by the sponsors gave the shelf life of the material as 'two years or more at ambient'. It was therefore considered stable for the duration of this study.

2. CONTROL SUBSTANCE

2.1 Identity of the control substance

The data for the control substance released for use in this experiment are tabulated below.

NAME	Carrier oil for SAP 011
BATCH NUMBER	3390 (Ref. 699519)
ST NUMBER	ST83/003
SOURCE	Shell Chemicals U.K. Ltd., Stanlow
DATE RECEIVED AT STL	11 January 1983
APPEARANCE	Golden brown oil
CHARACTERISATION	Flash point (P.M.C.C.)°C 215 Viscosity mm^2/s at 100°C 10.45
DATE RELEASED	10 February 1983

2.2 Storage of this control substance

Following its arrival in STL this control substance was stored in the dark at ambient temperature under nitrogen.

2.3 Stability of this control substance

The data sheet supplied by the sponsor gave the shelf life of the material as 'two years or more at ambient'. It was therefore considered stable for the duration of this study.

3. FORMULATION OF THE TEST AND CONTROL SUBSTANCES

Both test and control substances were dispensed undiluted into amber coloured glass bottles at approximately weekly intervals. They were assigned an expiry date of 1st January, 1985.

4. PREPARATION OF NONIDET P40 RINSE SOLUTIONS FOR POST-EXPOSURE SKIN WASHING

A solution containing 1 mg/ml (0.1% w/v) of NONIDET P40 in water was supplied weekly. The NONIDET P40, a non-ionic detergent was supplied by Shell Chemicals U.K. Ltd.

SHELL TOXICOLOGY LABORATORY (TUNSTALL)

Experiment
Number 2624

Title:-Appendix 2A - Individual bodyweights (g) of male rabbits over the 10 week exposure period

Experiment number 2624 Species :- Rabbit Sex :- Male

Appendix 2A - Individual bodyweights (g) of male rabbits over the 10 week exposure period

Body Weights

Treatment 1 CONTROL

Animal No.	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10
257	3352	3274	3292	3320	3376	3392	3410	3442	3426	3482	3530
260	4136	4002	4066	4066	4146	4060	3930	4128	3856	4086	4042
281	4380	4270	4318	4240	4354	4434	4470	4446	4500	4502	4570
383	4088	4060	4146	4114	4262	4264	4288	4306	4334	4380	4414
386	3714	3712	3718	3778	3858	3936	3690	3888	3912	3976	4026
391	4358	4294	4256	4278	4366	4428	4420	4442	4442	4402	
496	3662	3690	3710	3784	3840	3902	3864	3952	3946	3966	3992
508	3880	3880	3928	3974	4050	4042	4096	4110	4156	4206	4166
509	3424	3386	3400	3320	3350	3354	3350	3406	3372	3406	3424
511	3972	3970	4110	4114	4196	4244	4260	4248	4280	4310	4266
516	3696	3682	3710	3642	3734	3762	3796	3790	3816	3830	3844
527	3520	3494	3592	3602	3628	3660	3482	3634	3650	3666	3686

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Experiment number 2624 Species :- Rabbit Sex :- Male

Appendix 2A - Individual bodyweights (g) of male rabbits over the 10 week exposure period

Body Weights

Compound :- SAP 011

Treatment 2 [SAP 011]

Animal No.	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10
258	4084	4088	4134	4060	4040	4100	4108	4190	4216	4280	4256
384	4194	4212	4230	4216	4316	4342	4348	4336	4328	4322	4310
385	3862	3808	3900	3900	3962	3952	3966	4034	3978	4008	4034
493	3162	3150	3198	3126	3250	3234	3260	3274	3310	3332	3340
494	3588	3544	3613	3650	3704	3742	3750	3788	3762	3794	3800
495	3864	3912	3976	3980	4080	4144	4148	4176	4202	4222	4250
504	4260	4256	4226	4194	4190	4148	3978	4006	4016	3858	3976
510	3216	3226	3208	3252	3284	3340	3360	3400	3434	3426	3450
512	3362	3328	3420	3456	3504	3540	3522	3572	3552	3534	3536
514	3690	3718	3806	3832	3858	3890	3918	3888	3892	3902	3946
529	3672	3634	3588	3540	3616	3596	3602	3634	3590	3590	3584
530	4438	4250	4426	4440	4572	4620	4640	4666	4712	4720	4750

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SHELL TOXICOLOGY LABORATORY (TUNSTALL)

Experiment
Number 2624

Title:-Appendix 2B - Individual bodyweights (g) of male rabbits retained over the post-exposure period (weeks 11 - 22 inclusive)

Experiment number 2624 Species :- Rabbit Sex :- Male

Appendix 2B - Individual bodyweights (g) of male rabbits retained over the post-exposure period (weeks 11 - 22 inclusive)

Body Weights

Treatment 1 Control

Animal No.	Week 11	Week 12	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22
386	3972	4034	4054	4150	4130	4120	4166	4166	4178	4114	4114	4116
496	3976	3910	3830	3714	3686	3756	3786	3844	3846	3842	3882	3874
509	3490	3514	3392	3454	3452	3480	3484	3494	3498	3540	3530	3620
516	3830	3878	3876	3890	3900	3910	3936	3900	3904	3920	3892	3906
527	3660	3510	3654	3704	3720	3776	3770	3790	3786	3800	3816	3782

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riment number 2624 Species :- Rabbit Sex :- Male

ndix 2B - Individual bodyweights (g) of male rabbits retained over the post-exposure period (weeks 11 - 22 inclusive)

Body Weights

No. 22 Compound :- SAP 011

tment 2 [SAP 011]

al	Week 11	Week 12	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23
5	4036	4032	4032	4064	4102	4100	4046	4066	4066	4034	4030	4030	
5	4276	4336	4290	4330	4340	4340	4344	4352	4360	4392	4340	4326	
4	3882	4072	4166	4162	4120	4140	4180	4232	4240	4356	4390	4416	
2	3490	3490	3444	3454	3490	3484	3520	3560	3574	3650	3650	3670	
9	3550	3582	3542	3574	3580	3450	3456	3420	3410	3652	3644	3628	
0	4816	4840	4826	4900	4966	4946	4994	5000	5020	5066	5062	5070	

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SHELL TOXICOLOGY LABORATORY (TUNSTALL)

Experiment
Number 2624

Title:-Appendix 3A - Individual testes weights (g) of male rabbits killed immediately post exposure

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Experiment number 2624

Species:-Rabbit

Sex:-Male

Appendix 3A - Individual testes weights (g) of male rabbits killed immediately post exposure

Organ Weights

Week number:- 11

Date:-27/04/83

Animal No.	Initial body wt.	Terminal body wt.	Testes
Treatment 1 CONTROL			
257	3352	3520	5.101
260	4136	4030	5.947
281	4380	4610	5.595
383	4088	4412	6.576
508	3880	4180	6.224
511	3972	4196	6.578

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Experiment number 2624 Species:-Rabbit Sex:-Male

Appendix 3A - Individual testes weights (g) of male rabbits killed immediately post exposure

Organ Weights

Week number:- 11 Date:-27/04/83

Animal No.	Initial body wt.	Terminal body wt.	Testes
Treatment 2 [SAP 011]			
258	4084	4320	7.005
384	4194	4310	6.564
493	3162	3392	5.073
494	3588	3866	5.477
510	3216	3510	6.313
514	3690	3950	5.095

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SHELL TOXICOLOGY LABORATORY (TUNSTALL)

Experiment
Number 2624

Title:-Appendix 3B - Individual testes weights (g) of male rabbits killed at week 22 (12 weeks after end of exposure)

Experiment number 2624

Species:-Rabbit

Sex:-Male

Appendix 3B - Individual testes weights (g) of male rabbits killed at week 22 (12 weeks after end of exposure)

Organ Weights

Date:-21/07/83

Animal No.	Initial body wt.	Terminal body wt.	Testes
Treatment 1 Control			
386	3714	4134	5.538
496	3662	3872	6.926
509	3424	3506	5.504
516	3696	3856	4.650
527	3520	3730	6.124

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Experiment number 2624 Species:-Rabbit Sex:-Male

Appendix 3B - Individual testes weights (g) of male rabbits killed at week 22 (12 weeks after end of exposure)

Organ Weights

Week number:- 23 Date:-21/07/83

Animal No.	Initial body weight	Terminal body weight	Testes
Treatment 2			
[SAP 011]			
385	3862	3972	5.287
495	3864	4322	6.944
504	4260	4414	6.150
512	3362	3718	4.187
529	3672	3630	4.991
530	4438	5008	5.642

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Appendix 4 - Mating allocation of untreated females to treated males

Treatment group	Female No.	Male No.	Date mated	Female body weights (g) at day 0
2	486	493	25.4.83	4200
2	482	493	26.4.83	3988
1	565	281	25.4.83	4634
1	537	281	26.4.83	4280
1	559	516	25.4.83	5034
1	564	516	26.4.83	4240
2	558	504	25.4.83	4614
2	490	504	26.4.83	4252
2	481	494	25.4.83	4676
2	550	494	26.4.83	3376
2	487	495	25.4.83	4876
2	480	495	26.4.83	4256
1	554	257	25.4.83	4686
1	543	257	26.4.83	4292
2	674	258	25.4.83	4418
2	553	258	26.4.83	3850
1	687	260	25.4.83	4514
1	680	260	26.4.83	3980
2	489	529	25.4.83	4796
2	596	529	26.4.83	4010
1	546	527	25.4.83	4716
1	646	527	26.4.83	4008
1	474	383	25.4.83	4440
1	547	383	26.4.83	3850
2	542	384	25.4.83	4764
2	700	384	26.4.83	4184
2	636	385	25.4.83	4856
2	488	385	26.4.83	3944
1	694	386	25.4.83	4392
1	541	386	26.4.83	4200
2	675	514	25.4.83	4560
2	536	514	26.4.83	4126
1	699	511	25.4.83	4444
1	560*	511	26.4.83	4310
2	702	512	25.4.83	4630
2	693	512	26.4.83	4200
1	691	496	25.4.83	4420
1	555	496	26.4.83	4150
2	549	510	25.4.83	4412
2	638	510	26.4.83	3876
1	535	508	25.4.83	4420
1	595	508	26.4.83	4088
1	692	509	25.4.83	4466
1	701	509	26.4.83	3926
2	556	530	25.4.83	4380
2	548	530	26.4.83	4116

* The second female presented to M 511 was not receptive . . was replaced by F 560.

Experiment number 2624 Species:-Rabbit Duration days Compound: 1 = CONTROL 2 = SAP 011

Appendix 5 - Individual litter data of the untreated females mated to the treated males.

TERATOLOGY - Dam/Foetal Data

Treatment group	Dam no.	Aborted/ Pregnant/ Not pregnant	Killed or died	Necropsy date	Day Post-coitum	Live foetuses	No. of Resorptions	No. of Foetal deaths	No. of Left corp.lut.	No. of Right corp.lut.
1	474	Pregnant	Killed	24/05/83	29	08	00	00	02	08
1	535	Pregnant	Killed	24/05/83	29	04	01	00	08	04
1	537	Pregnant	Killed	25/05/83	29	08	01	00	06	04
1	541	Pregnant	Killed	25/05/83	29	08	00	00	03	05
1	543	Pregnant	Killed	25/05/83	29	05	00	00	06	03
1	546	Pregnant	Killed	24/05/83	29	02	00	00	04	08
1	547	Pregnant	Killed	25/05/83	29	00	04	00	04	07
1	554	Pregnant	Killed	24/05/83	29	12	00	00	03	09
1	555	Pregnant	Killed	25/05/83	29	07	00	00	05	05
1	559	Pregnant	Killed	24/05/83	29	11	02	00	06	07
1	560	Pregnant	Killed	25/05/83	29	07	02	00	03	06
1	564	Pregnant	Killed	25/05/83	29	02	00	00	05	06
1	565	Pregnant	Killed	24/05/83	29	14	00	00	06	09
1	595	Not pregnant	Killed	25/05/83	29					
1	646	Pregnant	Killed	25/05/83	29	06	00	01	03	10
1	680	Pregnant	Killed	25/05/83	29	02	01	00	05	08
1	687	Pregnant	Killed	24/05/83	29	11	00	00	08	04
1	691	Pregnant	Killed	24/05/83	29	11	01	00	05	09
1	692	Pregnant	Killed	24/05/83	29	09	00	00	05	08
1	694	Pregnant	Killed	24/05/83	29	10	01	01	13	02
1	699	Pregnant	Killed	24/05/83	29	09	01	01	07	05
1	701	Pregnant	Killed	25/05/83	29	09	01	00	09	03
2	480	Pregnant	Killed	25/05/83	29	08	00	00	06	05
2	481	Pregnant	Killed	24/05/83	29	04	00	00	05	06
2	482	Pregnant	Killed	25/05/83	29	03	02	00	03	06
2	486	Not pregnant	Killed	24/05/83	29					
2	487	Pregnant	Killed	24/05/83	29	08	00	00	04	05
2	488	Pregnant	Killed	25/05/83	29	12	00	00	06	07
2	489	Not pregnant	Killed	24/05/83	29					
2	490	Pregnant	Killed	25/05/83	29	07	00	00	05	03
2	536	Pregnant	Killed	25/05/83	29	09	02	00	05	09
2	542	Pregnant	Killed	24/05/83	29	08	00	01	06	04
2	548	Pregnant	Killed	25/05/83	29	11	00	00	04	07
2	549	Pregnant	Killed	24/05/83	29	13	01	01	09	09
2	550	Not pregnant	Killed	25/05/83	29					
2	553	Not pregnant	Killed	25/05/83	29					
2	556	Not pregnant	Killed	24/05/83	29	09	01	00	05	08
2	558	Pregnant	Killed	24/05/83	29	04	00	00	05	05
2	596	Pregnant	Killed	25/05/83	29	13	00	00	07	07
2	636	Pregnant	Killed	24/05/83	29	07	02	00	05	07
2	638	Pregnant	Killed	25/05/83	29					
2	674	Not pregnant	Killed	24/05/83	29	02	01	00	04	08
2	675	Pregnant	Killed	24/05/83	29					
2	693	Not pregnant	Killed	25/05/83	29	07	00	00	07	01
2	700	Pregnant	Killed	25/05/83	29	11	00	00	03	08
2	702	Pregnant	Killed	24/05/83	29					

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Appendix 6A - Individual macroscopic and microscopic findings of male rabbits killed after 10 weeks of dermal exposure to carrier oil or SAP 011

(Tissues in which no abnormal macroscopic or microscopic findings were recorded are not listed under Appendices 6A and 6B)

Treatment group carrier oil control

Rabbit number	Finding
257 M	External/general condition: good. Macroscopic findings: Heart: several depressed, gritty lesions on internal surface of aortic arch. Microscopic findings: Testes: hypoactive tubules <1%, pyknotic spermatid nuclei <1%, multinucleate spermatids <1%, single degenerate spermatocytes <1%, multiple degenerate spermatocytes <1%, mild inter-tubular fluid accumulation. Ductuli efferentes: focal interstitial lymphocyte infiltration; few multinucleate spermatids. Caput epididymis: small focus degenerate epithelial cells, few intra-epithelial cysts, small amounts intra-epithelial brown secretion; occasional spermatids and multinucleate spermatids, spermatozoa present. Cauda epididymis: occasional spermatids and multinucleate spermatids, spermatozoa present.
260 M	External/general condition: good. Macroscopic findings: Heart: 2 mm white lesion on internal surface of aortic arch - gritty texture. Skin: 1 cm necrotic area over left rib region. Microscopic findings: Testes: hypoactive tubules <1%, pyknotic spermatid nuclei <1%, multinucleate spermatids <1%, single degenerate spermatocytes <1%, multiple degenerate spermatocytes <1%, moderate intertubular fluid accumulation. Ductuli efferentes: focal lymphocytic and inflammatory cell aggregates; occasional spermatids and multinucleate spermatids. Caput epididymis: occasional small intra-epithelial cysts and intra epithelial brown secretion and degenerate cells; few spermatids, spermatocytes and multinucleate spermatids; occasional mitoses of epithelial cells; spermatozoa present, Cauda epididymis: occasional spermatids and multinucleate spermatids, spermatozoa present. Right caudal epididymal ligament: moderate inflammatory cell infiltration. Left caudal epididymal ligament: not found in section.

Appendix 6A - Contd.

Treatment group carrier oil control

Rabbit number	Finding
281 M	External/general condition: good. Microscopic findings: Testes: multinucleate spermatids 1%, atrophied tubules <1%, hypoactive tubules <1%, pyknotic spermatid nuclei <1%, single degenerate spermatocytes <1%, multiple degenerate spermatocytes <1%, mild focal intertubular fluid accumulation. Ductuli efferentes: lying adjacent to right ductuli is 2 mm mass of tissue composed of cells with eosinophilic vacuolated cytoplasm forming lobules which are separated by capillaries and contain large blood-filled spaces. This tissue is likely to be ectopic adrenal or embryonic tissue. Occasional spermatids, spermatocytes and and multinucleate spermatids. Vas deferens: occasional spermatids. Caput epididymis: occasional mitoses and pyknotic nuclei of epithelium, multinucleate spermatids and moderate numbers of spermatids; moderate amount of intra-epithelial brown secretion, spermatozoa present. Cauda epididymides occasional spermatids, one tubule shows pyknotic nuclei; spermatozoa present. Vas deferens: few spermatids. Caudal epididymal ligament: no lesions in right ligament, left ligament not found in section.
383 M	External/general condition: good. Microscopic findings: Testes: atrophy of seminiferous tubules 3%, hypoactive tubules 1%, pyknotic spermatid nuclei <1%, multinucleate spermatids 2%, single degenerate spermatocytes <1%, multiple degenerate spermatocytes <1%, sloughing of epithelium <1%, mild intertubular fluid accumulation of left testis. Ductuli efferentes: moderate numbers of spermatids and multinucleate spermatids and spermatocytes; left ductuli show mild focal interstitial lymphocytic infiltration. Caput epididymis: occasional mitoses of epithelial cells, moderate numbers of spermatids, spermatocytes and multinucleate spermatids; spermatozoa present. Cauda epididymis: moderate numbers of spermatids, spermatocytes and multinucleate spermatids, spermatozoa present. Vas deferens: occasional spermatids. Caudal epididymal ligament: marked inflammatory cell infiltration of right ligament.

Contd...

Appendix 6A - Contd.

Treatment group carrier oil control

Rabbit number	Finding
508 M	External/general condition: good. Macroscopic findings: Heart: 2 mm depressed gritty lesion on internal surface of aortic arch. Microscopic findings: Testes: atrophied tubules <1%, hypoactive tubules <1%, multinucleate spermatids 2%, pyknotic spermatid nuclei <1%, single degenerate spermatocytes <1%, sloughing of epithelium of right testis <1%, mild focal intertubular fluid accumulation. Ductuli efferentes: occasional spermatids and multinucleate spermatids. Caput epididymis: rare necrotic epithelial cells, occasional mitoses, fine cytoplasmic vacuolation of the epithelium; moderate numbers of spermatids and occasional multinucleate spermatids, spermatozoa present. Cauda epididymis: occasional spermatids, spermatozoa present. Vas deferens: occasional spermatids. Caudal epididymal ligament: moderate inflammatory cell infiltration in left ligament.
511 M	General/external condition: good. Microscopic findings: Testes: atrophied seminiferous tubules <1%, hypoactive seminiferous tubules 2%, multinucleate spermatids <1%, pyknotic spermatid nuclei <1%, single degenerate spermatocytes <1%, multiple degenerate spermatocytes <1%, mild intertubular fluid accumulation. Ductuli efferentes: occasional spermatids and spermatocytes. Caput epididymis: moderate numbers of spermatids and multinucleate spermatids, occasional necrotic epithelial cells and associated inflammatory cells. Intertubular inflammatory cell focus; occasional mitoses of epithelial cells; spermatozoa present. Cauda epididymis: focal cytoplasmic vacuolation of epithelium, moderate spermatids and occasional multinucleate spermatids; spermatozoa present. Vas deferens: occasional spermatids. Caudal epididymal ligament: focal small round cell aggregate in left ligament.

Contd...

Appendix 6A - Contd.

Treatment group - SAP 011

Rabbit number	Finding
258 M	External/general condition: good. Macroscopic findings: Heart: focal white gritty lesions on internal surface of aortic arch. Microscopic findings: Testes: hypoactive tubules <1%, pyknotic spermatid nuclei <1%, single degenerate spermatocyte <1%, multiple degenerate spermatocytes <1%, multinucleate spermatids <1%; mild intertubular fluid accumulation. Ductuli efferentes: small focus ectopic adrenal tissue or embryonic tissue next to ductuli. Rare spermatids/ spermatocytes. Caput epididymis: occasional mitoses of epithelium, few small intra epithelial cysts; occasional intra-epithelial brown secretion. Small numbers of spermatids seen in lumen; spermatozoa present. Cauda epididymis: occasional spermatid, spermatocytes and multinucleate spermatids; spermatozoa present. Vas deferens: rare spermatid nuclei. Caudal epididymal ligament: mild inflammatory cell infiltration in right ligament; left ligament not found in section.
384 M	External/general condition: good. Microscopic findings: Testes: atrophic tubules <1%, hypoactive tubules <1%, pyknotic spermatid nuclei <1%, single degenerate spermatocytes <1%, multiple degenerate spermatocytes <1%, multinucleate spermatids <1%; mild intertubular fluid accumulation. Ductuli efferentes: occasional foci of interstitial inflammatory cells and focus of necrotic epithelial cells in one ductule; occasional multinucleate spermatids. Caput epididymis: occasional mitoses of epithelium; few small intra epithelial cysts and small amount intra epithelial brown secretion; rare necrotic epithelial cells; moderate spermatozoa spermatids, spermatocytes and multinucleate spermatids. Cauda epididymis: occasional spermatids and moderate multinucleate spermatids; spermatozoa present. Caudal epididymal ligament: mild inflammatory cell infiltration in right ligament and moderate inflammatory cells and occasional degenerate muscle fibre in left ligament.

Appendix 6A - Contd.

Treatment group - SAP 011

Rabbit number	Finding
493 M	External/general condition: good. Macroscopic findings: Lungs: left, right apical, right cardiac, right diaphragmatic, right azygos - slightly patchy. Microscopic findings: Testes: hypoactive tubules <1%, pyknotic spermatid nuclei <1%, multinucleate spermatids <1%, single degenerate spermatocytes <1%, multiple degenerate spermatocytes <1%, mild intertubular fluid accumulation in right testis. Ductuli efferentes: left ductuli show 1 mm mass of tissue composed of cells with eosinophilic and mildly vacuolated cytoplasm in lobules, separated by capillaries. This tissue is likely to be ectopic adrenal or embryonic tissue. Rare spermatids/spermatocytes. Caput epididymis: occasional mitoses, spermatids and multinucleate spermatids, spermatozoa present. Cauda epididymis: spermatozoa present. Caudal epididymal ligament: moderate inflammatory cell infiltration of left ligament.
494 M	External/general condition: good. Microscopic findings: Testes: multinucleate spermatids 6%; multiple degenerate spermatocytes 1%, single degenerate spermatocytes <1%, pyknotic spermatid nuclei <1%, hypoactive seminiferous tubules <1%, atrophic seminiferous tubules <1%, intertubular fluid present focally in small amounts. Ductuli efferentes: few spermatids and multinucleate spermatids. Caput epididymis: occasional mitoses of epithelium and occasional necrotic epithelial cells, moderate spermatids and multinucleate spermatids, spermatozoa present. Cauda epididymis: moderate numbers of spermatids, spermatocytes and multinucleate spermatids, spermatozoa present. Caudal epididymal ligament: marked inflammatory cell infiltration in right ligament.

Contd...

Appendix 6A - Contd.

Treatment group - SAP 011

Rabbit number	Finding
510 M	External/general condition: good. Microscopic findings: Testes: atrophic tubules 3%, hypoactive tubules 2%, pyknotic spermatid nuclei 1%, multinucleate spermatids 2%, multiple degenerate spermatocytes <1%, single degenerate spermatocytes <1%; sloughing of epithelium of left testis <1%, mild intertubular fluid accumulation. Ductuli efferentes: few spermatids in lumen. Caput epididymis: occasional mitoses in epithelial cells; few spermatids and multinucleate spermatids; few necrotic epithelial cells; spermatozoa present. Cauda epididymis: few spermatids; spermatozoa present. Caudal epididymal ligament: no lesions.
514 M	External/general condition: good. Microscopic findings: Testis: hypoactive tubules 1%, pyknotic spermatids <1%, multinucleate spermatids 2%, single degenerate spermatocyte <1%, mild intertubular fluid accumulation. Ductuli efferentes: small focus periductular inflammatory cells; few spermatids. Caput epididymis: few intra epithelial cysts and brown secretion, few inflammatory cell infiltrates, occasional mitoses in epithleium, moderate numbers of spermatids and occasional multinucleate spermatids; spermatozoa present. Cauda epidydimis: few spermatids and multinucleate spermatids; spermatozoa present. Caudal epididymal ligament: mild inflammatory cell infiltration of right ligament.

Appendix 6B - Individual macroscopic and microscopic findings of male rabbits killed approx. 12 weeks after end of dermal exposure to carrier oil or SAP 011

Treatment group - carrier oil control

Rabbit number	Finding
386 M	External/general condition: Good. Hair has poor growth on neck region where dermal exposure was carried out. Macroscopic findings: Heart: aortic arch shows multiple white depressions on internal surface. Microscopic findings: Testes: focal mild intertubular fluid, atrophic tubules <1%, hypoactive tubules <1%, tubules showing pyknotic spermatid nuclei <1%, tubules showing single degenerate spermatocytes <1%, tubules showing multiple degenerate spermatocytes <1%, multinucleate spermatids <1%, sloughing of germinal epithelium <1%, rare degenerate spermatogonia in one testis. Ductuli efferentes: moderate numbers of spermatids and spermatocytes. Tissue fixed in Regaud's solution showed no ectopic adrenal/embryonic tissue. Caput epididymis: rare small intra-epithelial cysts, mild intra-epithelial brown secretion, occasional mitoses of epithelium, occasional intra luminal spermatids; spermatozoa present. Cauda epididymis: mild spermatids/spermatocytes; spermatozoa present. Caudal epididymal ligament: mild inflammatory cell infiltration, small round cell aggregates.
391 M	See Tables 5B and 6B for macroscopic and microscopic findings.
496 M	External/general condition: Good. Hair has poor growth on neck region where dermal exposure took place. Macroscopic findings: Kidneys: right kidney very small (1.5 cm long), renal pelvis contains calculi. Left kidney moderately large. Microscopic findings: Testes: mild focal intertubular fluid. Atrophic tubules <1%, hypoactive tubules 1%, tubules showing pyknotic spermatid nuclei <1%, tubules showing single degenerate spermatocytes <1%, tubules showing multiple degenerate spermatocytes <1%, tubules with sloughing of epithelium <1%.

Appendix 6B - Contd.

Treatment group - carrier oil control

Rabbit number	Finding
496 (Contd.)	Ductuli efferentes: small numbers spermatids/spermatocytes. Caput epididymides: rare degenerate epithelial cells occasionally with inflammatory cells, rare intra-epithelial cysts. Occasional mitoses of epithelial cells; occasional intra luminal spermatids, normal spermatozoa. Cauda epididymis: rare spermatids, spermatocytes and multinucleate spermatids, normal spermatozoa. Vas deferens: rare spermatids. Caudal epididymal ligament: few small round cell aggregates.
509 M	External/general condition: good. Poor hair growth in area where dermal exposure took place. Microscopic findings: Testes: mild focal intertubular fluid, atrophic tubules <1%, hypoactive tubules 1% tubules showing pyknotic spermatid nuclei <1%, tubules with single degenerate spermatocytes <1%, tubules with multinucleate spermatids <1%. Ductuli efferentes: small numbers of spermatids/spermatocytes. Caput epididymis: small intra-epithelial cysts, mild intra-epithelial brown secretion, occasional spermatids; normal spermatozoa. Cauda epididymis: mild spermatids, spermatocytes, multinucleate spermatids, normal spermatozoa.
516 M	External/general condition: Good. Microscopic findings: Testes: atrohpic tubules 1%, hypoactive tubules 2%, tubules showing single degenerate spermatocytes <1%, tubules showing multiple degenerate spermatocytes <1%, tubules showing multinucleate spermatids <1%. Rare degenerate spermatogonia in one testis. Ductuli efferentes: small numbers of spermatids, spermatocytes and multinucleate spermatids. Bilateral foci of ectopic adrenal/embryonic tissue. Tissue fixed in Regaud's solution showed no ectopic adrenal/embryonic tissue. Caput epididymis: rare degenerate epithelial cells; occasional small intra-epithelial cysts; occasional spermatids in lumina; normal spermatozoa. Cauda epididymis: occasional spermatids and spermatocytes; normal spermatozoa. Caudal epididymal ligament: mild inflammatory cell infiltration.

Appendix 6B - Contd.

Treatment group - carrier oil control

Rabbit number	Finding
527 M	External/general condition: good. Microscopic findings: Testes: mild focal intertubular fluid, atrophic tubules <1%, hypoactive tubules 1%, tubules with pyknotic spermatid nuclei <1%, tubules with single degenerate spermatocytes <1%, tubules with multiple degenerate spermatocytes <1%, tubules showing multinucleate spermatids <1%. Ductuli efferentes: small numbers of spermatids, spermatocytes and multinucleate spermatids. Tissue fixed in Regaud's solution showed no ectopic adrenal embryonic tissue. Caput epididymis: rare degenerate epithelial cells with inflammatory cells. Small intra-epithelial cysts, mild intra-epithelial brown secretion, occasional mitoses and intra-epithelial spermatids, mineralised tubule seen; normal spermatozoa. Cauda epididymis: rare spermatids, normal spermatozoa. Vas deferens: rare spermatids. Caudal epididymal ligament: mild inflammatory cell infiltration; small round cell aggregates.

Contd....

Appendix 6B - Contd.

Treatment group - SAP 011

Rabbit number	Finding
385 M	External/general condition: Good. Microscopic findings: Testes: mild intertubular fluid accumulation, atrophic tubules <1%, hypoactive tubules 2%, tubules showing pyknotic nuclei <1%, tubules showing single degenerate spermatocytes <1%, tubules with multinucleate spermatids <1%, tubules with sloughing of epithelium <1%. Caput epididymis: rare degenerate epithelial cells; occasional small intra-epithelial cysts; occasional mitoses of epithelial cells; occasional, multinucleate spermatids; mild intra-epithelial brown secretion; normal spermatozoa. Cauda epididymis: rare spermatids/spermatocytes, normal spermatozoa present. Ductuli efferentes: rare spermatids.
495 M	External/general condition: good. Microscopic findings: Testes: mild focal intertubular fluid, hypoactive tubules 1%, tubules showing pyknotic spermatid nuclei <1%, tubules showing single degenerate spermatocytes <1%, tubules showing multiple degenerate spermatocytes <1%, tubules showing multinucleate spermatids <1%, tubules showing sloughing of epithelium <1%. Ductuli efferentes: small numbers spermatids/spermatocytes in lumina; focus of ectopic adrenal/embryonic tissue. Tissue fixed in Regaud's solution showed no ectopic adrenal/embryonic tissue. Caput epididymis: rare degenerate epithelial cells occasionally with inflammatory cells. Rare small intra-epithelial cysts. Occasional epithelium mitoses and intra-luminal spermatids; normal spermatozoa. Cauda epididymis: rare spermatids/spermatocytes; normal spermatozoa. Vas deferens: rare spermatids in lumen. Caudal epididymal ligament: moderate inflammatory cell infiltration.

Appendix 6B - Contd.

Treatment group - SAP 011

Rabbit number	Finding
504 M	External/general condition: Good. Macroscopic findings: Heart: aortic arch shows small white fibrous lesions on internal surface. Microscopic findings: Testes: mild focal intertubular fluid; tubule with rare degenerate spermatogonia; atrophic tubules <1%, hypoactive tubules 3%, tubules showing pyknotic spermatid nuclei <1%, tubules showing single degenerate spermatocytes <1%, tubules showing multiple degenerate spermatocytes <1%, tubules showing multinucleate spermatids <1%. Ductuli efferentes: small numbers of spermatids/spermatocytes. Tissue fixed in Regaud's solution showed no ectopic adrenal/ embryonic tissue. Caput epididymis: moderate intra-epithelial brown secretion, occasional mitoses, occasional spermatids in lumen; spermatozoa present. Cauda epididymis: mild spermatids/spermatocytes; normal spermatozoa. Vas deferens: rare or occasional spermatids. Caudal epididymal ligament: moderate inflammatory cell infiltration.
512 M	External/general condition: good. Microscopic findings: Testes: mild inter-tubular fluid accumulation in one testis; atrophic tubules <1%, hypoactive tubules <1%, tubules showing pyknotic spermatid nuclei <1%, tubules showing single degenerate spermatocytes <1%; tubules showing multiple degenerate spermatocytes <1%, multi-nucleate spermatids <1%, tubules with sloughing of epithelium <1%, rare degenerate spermatogonia in one tubule. Ductuli efferentes: occasional multinucleate spermatids. Caput epididymis: occasional mitoses of epithelium, occasional spermatids and multinucleate spermatids; normal spermatozoa. Cauda epididymis: rare spermatids, spermatocytes and multinucleate spermatids; normal spermatozoa. Caudal epididymal ligament: moderate inflammatory cell infiltration in 1 ligament.

000063

Contd...

Appendix 6B - Contd.

Treatment group - SAP 011

Rabbit number	Finding
529 M	External/general condition: Good. Microscopic findings: Testes: mild focal intertubular fluid. Atrophic tubules 1%, hypoactive tubules 5%. Tubules showing pyknotic spermatid nuclei <1%, tubules showing single degenerate spermatocytes <1%, tubules showing multinucleate spermatids <1%. Ductuli efferentes: small numbers of spermatids/spermatocytes, focus of adjacent ectopic adrenal/embryonic tissue. Tissue fixed in Regaud's solution showed no ectopic adrenal/embryonic tissue. Caput epididymis: rare pyknotic epithelial cells occasionally with inflammatory cells, rare small intra epithelial cysts, occasional spermatids, mild intra epithelial brown secretion; normal spermatozoa. Cauda epididymis: rare spermatids and spermatocytes, rare multinucleate spermatids, focal cytoplasmic vacuolation of epithelium; normal spermatozoa. Caudal epididymal ligament: one ligament not examined, the other ligament showed mild inflammatory cell infiltration.
530 M	External/general condition: good. Macroscopic findings: Heart: aortic arch shows minute depressed foci on internal surface. Microscopic findings: Testes: mild focal intertubular fluid, hypoactive tubules <1%, tubules showing pyknotic spermatid nuclei <1%, tubules showing single degenerate spermatocytes <1%, tubules showing multiple degenerate spermatocytes <1%, multinucleate spermatids 2%; tubule with rare degenerate spermatogonia. Ductuli efferentes: rare multinucleate spermatids in lumina. Caput epididymis: rare degenerate epithelial cells; occasional small intra-epithelial cysts and mild brown secretion; occasional fine cytoplasmic vacuolation of epithelium; occasional spermatids and multinucleate spermatids; normal spermatozoa. Cauda epididymis: rare multinucleate spermatids; normal spermatozoa. Caudal epididymal ligaments: moderate inflammatory cell infiltration.

Appendix 7 - Individual macroscopic findings of non-pregnant female rabbits

Treatment group of male	Female number	Mated with male no.	Findings
1	595	508	Lungs have mottled appearance.
2	486	493	Paraovarian cyst (left).
2	489	529	Fallopian tube cyst.
2	550	494	None.
2	553	258	None.
2	556	530	Vaginal/cervical area contains cloudy fluid.
2	674	258	None.
2	693	512	None.

Appendix 7 - Individual macroscopic findings of non-pregnant female rabbits

Treatment group of male	Female number	Mated with male no.	Findings
1	595	508	Lungs have mottled appearance.
2	486	493	Paraovarian cyst (left).
2	489	529	Fallopian tube cyst.
2	550	494	None.
2	553	258	None.
2	556	530	Vaginal/cervical area contains cloudy fluid.
2	674	258	None.
2	693	512	None.

QUALITY ASSURANCE STATEMENT

REPORT NUMBER: SBER.84.002

EXPERIMENT NUMBER: 2624

REPORT TITLE: TOXICITY STUDIES ON OIL ADDITIVES: ONE GENERATION REPRODUCTION STUDY IN MALE RABBITS REPEATEDLY TREATED DERMALLY WITH SAP 011 FOR 10 WEEKS

STUDY DIRECTOR: K. M. Dix

The conduct of this study was inspected and this report has been audited to ensure that it accurately describes the methods used and that the reported results accurately reflect the raw data of the study.

	Date of inspection or audit	Date of written QA report to management
Study conduct:	15.02.83	31.05.83
	17.03.83	31.05.83
	25.04.83	31.05.83
	27.04.83	31.05.83
	24.05.83	31.05.83
	22.07.83	26.07.83
Final report:	27.1.84	27.1.84

H. R. RODERICK

QUALITY ASSURANCE INSPECTOR

SBER.84.002

TOXICITY STUDIES ON OIL ADDITIVES: ONE GENERATION REPRODUCTION STUDY IN MALE RABBITS REPEATEDLY TREATED DERMALLY WITH SAP 011 FOR 10 WEEKS

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INDEX TERMS: 10. CHEMICALS
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KEYWORDS: Dermal; male; rabbit; reproduction; SAP011; oil additive

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