8EHQ-0698-14205

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CONDEA VISTA

June 16, 1998

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Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
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Washington, DC 20460

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ATTN: 8(e) Coordinator

Subject: Section 8(e) Submission

Dear Sir or Madam:

This submission is provided on behalf of CONDEA Vista Company (CONDEA Vista) in accordance with section 8(e) of the Toxic Substances Control Act. It presents the results of a two generation reproductive toxicity study conducted on 1,2-benzenedicarboxylic acid, di-C_{6-10}- alkyl esters (CAS No. 68515-51-5) referred to in the report as WITAMOL 110/LINPLAST 610P. The details of this study and its findings are provided in the enclosed draft report. A summary of the study (pages 11 and 12 of the draft report) is also attached.

This study was co-sponsored by Hüls Aktiengesellschaft and CONDEA Chemie GmbH. Both CONDEA Chemie and CONDEA Vista are wholly-owned subsidiaries of RWE-DEA. CONDEA Vista manufacturers VISTA 610P PLASTICIZER, which is similar in composition to 1,2-benzenedicarboxylic acid, di-C_{6-10}- alkyl esters, at only one site in the US.

Under normal manufacturing and compounding conditions there is little or no potential for employee exposure to VISTA 610P PLASTICIZER. In the event of anticipated exposures, recommended protective procedures include the use of chemical goggles and wearing full protective clothing, including boots and gloves. Mechanical ventilation is also recommended if handling the material in enclosed spaces or at elevated temperatures. In cases where additional respiratory protection is required, it is recommended workers use NIOSH-approved organic vapor air-purifying respirators, self-contained breathing apparatus, or air-supplied respirators.

Incorporation of VISTA 610P PLASTICIZER into the plastic matrix limits its potential for significant human exposure in downstream applications. The low aqueous solubility of long-chain phthalate esters indicates a low potential for humans to be exposed to significant levels of VISTA 610P PLASTICIZER via water. This property would also impede its ability to leach from waste disposal sites.

Based on the protective procedures that CONDEA Vista has in place, the physical/chemical properties of CONDEA Vista 610P PLASTICIZER, and the fact that it is usually encased in a

plastic matrix during use, we do not believe that this study provides any reason for a significant health concern associated with its continued manufacture and use.

Any questions about this submission should be directed to the undersigned as indicated.

Respectfully submitted,

Dave Penney

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SUMMARY

Toxicity in adult male animals dosed at 10000 p.p.m. was manifest by reductions in weight gain in all generations and by reduced food consumption in the F_0 and F_1 generations. There was some reduction in food consumption during lactation among females at 10000 p.p.m.

There were no obvious effects of treatment on the mating performance, fertility indices or duration of gestation.

At 10000 p.p.m. litter survival was slightly decreased across Days 4 to 21, and there were slight decreases in pup and litter weights. Pup survival, and litter and pup weights at the lower levels were similar to Control.

Taking the 2 generations together, it was considered that there was a marginal delay in sexual maturity at 10000 p.p.m., but that sexual maturity at the lower levels was attained at a similar age to that of Controls.

At 10000 p.p.m., mean absolute testes weights among adults were similar to Control; adjusted weights for F_1 adults were slightly increased, while weights for weanlings at this level were slightly decreased. The weights of seminal vesicles in adults at 10000 p.p.m. were reduced, and this reduction extended to F_2 adults at 3000 p.p.m. Mean prostate weight was reduced among F_1 adults at 10000 p.p.m.

There were no effects noted on the tubule diameter or distribution of tubule stages noted in the testes.

Mean kidney weights of females at 3000 and 10000 p.p.m. were increased in the F_0 and F_1 generations, and there was a slight increase among F_1 females at 1000 p.p.m. Kidney weights of F_1 males at 3000 and 10000 p.p.m. were also increased.

Liver weights of females at 3000 and 10000 p.p.m. were increased; liver weights of F_0 and F_2 males at these levels were also increased, but weights for F_1 males were similar to Control. Liver weights of F_1 females at 1000 p.p.m. were increased. At necropsy, most adult males at 10000 p.p.m. had necropsy findings in the liver, including discoloured, enlarged and pale liver with prominent lobulation and/or pale/dark focus. Pale liver foci were also observed for occasional males at 3000 p.p.m. and for occasional females at 10000 p.p.m. Most F_0 and F_1 males at 10000 p.p.m. had histological findings in the liver, including generalised cellular change, basophilic foci(us), vacuolated focus, eosinophilic cell focus, clear cell focus, bile duct hyperplasia and Kupffer-cell pigmentation.

In conclusion, the no effect level for reproductive effects was considered to be 3000 p.p.m. It was not possible to identify a no effect level in this study, although effects at 1000 p.p.m. were confined to increased liver and kidney weights among F_1 females.

Inveresk Report No. 15380

WITAMOL 110/LINPLAST 610 P
TWO GENERATION REPRODUCTION STUDY IN RATS

Inveresk Project No. 491603

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CONFIDENTIAL

Inveresk Report No. 15380

WITAMOL 110/LINPLAST 610 P
TWO GENERATION REPRODUCTION STUDY IN RATS

Inveresk Project No. 491603

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Total Number of Pages: 470

AUTHENTICATION

'I, the undersigned, hereby declare that this work was performed under my direction and in accordance with the principles of Good Laboratory Practice. The study was conducted according to the procedures herein described and this report represents a true and accurate record of the results obtained.'

S J Barton BA MSc DABT
Study Director

Date:

DRAFT REPORT No. 15380

On receipt of approval or amendments, or 16 weeks from today's date if no amendments have been requested, Inveresk reserves the right to despatch the final report.

Inveresk reserves the right to make additional charges for a review of data, amendments or for corrections of minor errors following issue of the final report.

For the final report, this page will be replaced by the Quality Assurance Statement.

Inveresk Research

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SUMMARY

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Taking the 2 generations together, it was considered that there was a marginal delay in sexual maturity at 10000 p.p.m., but that sexual maturity at the lower levels was attained at a similar age to that of Controls.

At 10000 p.p.m., mean absolute testes weights among adults were similar to Control; adjusted weights for F_1 adults were slightly increased, while weights for weanlings at this level were slightly decreased. The weights of seminal vesicles in adults at 10000 p.p.m. were reduced, and this reduction extended to F_2 adults at 3000 p.p.m. Mean prostate weight was reduced among F_1 adults at 10000 p.p.m.

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INTRODUCTION

The test material, Witamol 110/Linplast 610 P was accepted from Hüls AG, Marl, Germany to evaluate the effects on general reproductive performance when the test material was administered through 2 complete reproductive cycles. This report describes the methods used and the results obtained in the study, which was carried out at the Elphinstone Research Centre of Inveresk Research (Inveresk).

This two generation reproduction study in rats is part of a programme of experiments designed to evaluate the toxicity of the test material to reproduction in experimental animals.

The rat is a standard rodent species for the testing in animals required by regulatory authorities, and the normal processes of reproduction and development in rats are well documented in this laboratory.

The oral route of test material administration (*via* the diet) has been specified because it is a route of possible human exposure.

The key dates for this study were:

Protocol Signed by Study Director:	8 July 1996
Animal Arrival:	23 July 1996
First Day of Dosing:	5 August 1996
Date of Final Necropsy:	22 May 1997
Study Completion Date:	See Authentication page for date of Study Director's signature

All data generated and recorded during this study, including a copy of the final report, will be stored in the Scientific Archives of Inveresk Research for 5 years after issue of

the final report. At the end of the 5 year period the Sponsor will be consulted regarding the disposal or continued storage of raw data.

EXPERIMENTAL PROCEDURE

TEST MATERIAL

A delivery of 20 litres of Witamol 110/Linplast 610 P, Batch No. 950608 was received at Inveresk on 2 August 1995. The test material, a colourless liquid, was stored in the dark at ambient temperature in the Inveresk dispensary. For reporting purposes the test material will be referred to as 610 P. A copy of the certificate of analysis is reproduced in Appendix 1.

ANIMALS

One batch of 120 male and 120 female Sprague-Dawley rats of the Charles River CD strain (outbred albino) was obtained from Area 57 of Charles River (UK) Limited, Margate, Kent, England, to provide 112 rats of each sex for the study. The animals were *ca* 4 weeks of age. A sample of male animals weighed 84-104 g and a sample of females weighed 57-95 g. No more than 2 males or 2 females were derived from any one source litter, siblings being identified.

All the animals were clinically examined on arrival for signs of abnormality or disease. No such signs were found and the animals were accepted for use in the study.

The animals were acclimatised in the Inveresk animal room for 13 days prior to the commencement of treatment.

The 8 animals of each sex that were not allocated to treatment groups were not regarded as part of the study.

ANIMAL MANAGEMENT

Room Environment and Sanitation

The study was conducted in Room L34 of the rodent toxicology accommodation at the Elphinstone Research Centre of Inveresk Research.

There was automatic control of light cycle, temperature and humidity. Light hours were 0700-1900 h. Target ranges for temperature and relative humidity were 20°C ± 2°C and 50% ± 15% respectively, with 15-20 air changes per hour. There was continuous monitoring of temperature and relative humidity, which indicated only minor departures from the target ranges. None of the observed departures from the normal ranges were considered to have affected the outcome of the study.

Each day, on completion of all other work, the floor was swept and then mopped with a 0.5% solution of Tego 2000 (Th Goldschmidt Limited, Victoria, Ruislip, Middlesex, UK), an amphoteric biocide/cleanser. The room was washed with this solution once weekly.

Caging and Cage Sanitation

The F_0 animals were initially housed 2 per cage in polypropylene cages with stainless steel grid bottoms, mesh tops and food hoppers. The cages measured 58 x 38.5 x 20 cm and were suspended on racks containing 5 rows of 3 cages. Males and females were racked separately. Excreta were collected on a tray lined with absorbent paper, suspended beneath each cage.

Three days prior to the initiation of mating, the males were transferred to individual grid bottomed cages. For mating, the females were transferred to the cage of the appropriate co-group male.

Mated females were transferred to individual solid bottomed cages measuring 42 x 27 x 20 cm, in which sterilised white wood shavings were provided as bedding (see Appendix 2 for certificate). White paper tissue was supplied to each mother for incorporation in the nest; this was replaced when it became soiled. Dams and their litters retained this type of cage until termination.

F_1 animals selected as parents of the next generation, and selected F_2 animals up to termination, were housed 2 per cage in polypropylene cages with stainless steel grid bottoms, mesh tops and food hoppers. The cages measured 58 x 38.5 x 20 cm and were suspended on racks containing 5 rows of 3 cages. Males and females were racked separately. Excreta was collected on a tray lined with absorbent paper, suspended beneath each cage.

Each cage was provided with a polycarbonate water bottle, with a Durethan™ cap and stainless steel tip.

Cages, absorbent papers and water bottles were regularly changed. Clean wood shavings were provided at each change of solid bottomed cage.

Diet and Water

Rat and Mouse Breeder Diet No. 3 SQC (Expanded) Fine Ground, was supplied by Special Diets Services Limited (SDS), Stepfield, Witham, Essex, UK and was available to the rats *ad libitum*. The diet was supplied with batch analyses, and the analysis of a typical batch used during the study is given in Appendix 3.

The animals had access to domestic mains water *ad libitum*. The supply is analysed regularly for dissolved and suspended materials, and a typical, recent analysis is given in Appendix 4.

None of the contaminants revealed by the analysis of diet and water were considered to have affected the outcome of this study.

TREATMENT

Allocation of Animals to Treatment Groups

On arrival from the supplier, the animals were allocated to treatment groups using a computer generated series of randomly sequenced numbers representing the treatment groups. It was ensured in this process that siblings were not placed in the same treatment group. Cages in any one treatment group were evenly distributed through the caging system.

Animal Identification

Each F_0 and F_1 adult animal and each F_2 animal retained for post-weaning investigations received a unique earmark which identified it individually within the study and corresponded to the number of that animal. Each of these animals was ascribed a cage card which was colour coded for treatment group and marked with the relevant treatment, the project, cage and animal numbers, sex and the litter derivation. Pre-weanlings were not individually identified and were referred to under their mother's number.

The treatment groups and animal numbers were arranged as follows:

Group Number	Treatment	Animal Numbers					
		F_0 Males	F_0 Females	F_1 Males	F_1 Females	F_2 Males	F_2 Females
1	Control	1-9,830[a],11-28	113-140	301-324	401-424	801-823	901-923
2	Low dose	29-56	141-168	325-348	425-448	825-847	925-947
3	Intermediate dose	57-84	169-196	349-372	449-472	849-871	949-971
4	High dose	85-96,260[b],98-112	197-224	373-396	473-496	873-895	973-995

a = Animal 10 renumbered as 830
b = Animal 97 replaced by Animal 260

Testes weights only were recorded from animals numbered as detailed below:

Group Number	Treatment	Animal Numbers	
		F_1 Males	F_2 Males
1	Control	613-640	1101-1124
2	Low dose	641-668	1125-1148
3	Intermediate dose	669-696	1149-1172
4	High dose	697-724	1173-1196

Dose Levels

The following dose levels were used during the study:

Group Number	Treatment	p.p.m. 610 P
1	Control	0
2	Low dose	1000
3	Intermediate dose	3000
4	High dose	10000

Dose levels were agreed with the Sponsor after evaluation of existing relevant toxicological data.

Treatment Regime

The test material was administered orally, by admixture with the diet. The diet contained a constant concentration of test material and was available continuously to the animals *ad libitum*.

Commencing at *ca* 6 weeks of age, F_0 animals were treated for 10 weeks prior to mating for the production of the F_1 litters. Treatment continued throughout the mating, gestation and lactation periods until termination after weaning of these litters.

F_1 animals were weaned onto the same diets as were fed to their respective parents. The selected F_1 animals were treated for *ca* 11 weeks after weaning, prior to mating. Treatment then continued for both sexes throughout the mating, gestation and lactation periods, until termination at the time of weaning of the F_2 litters. The selected

F_2 animals were treated until termination on the completion of the post-weaning assessments.

Preparation of Formulated Diets

Work performed on the validation of the analytical method revealed that the diet was stable for 14 days. Fresh batches of treated diets were prepared weekly for most of the study, but towards the end of the study, where only small amounts of diet were required, diet was prepared less frequently but used within 14 days of formulation.

A premix of a suitable concentration (50000 p.p.m. 610 P) was prepared by dissolving the appropriate amount of test material in a suitable volume of acetone, and then adding the acetone solution to untreated diet. This premix was mixed for *ca* 1 h with fan-assisted venting to remove the acetone. For the High dose level, the requisite quantity of premix was added to the appropriate amount of untreated diet and blended. For the Low and Intermediate dose levels, the appropriate quantity of High dose level diet was added to untreated diet and then similarly blended. Each final formulation was blended for *ca* 20 min in a Winkworth change drum mixer. Each mixed batch was stored in a closed container at ambient temperature.

The Control diet was prepared in the same manner as the high dose diet, but without addition of test material.

Analysis of Formulated Diets

On 5 occasions, triplicate samples were taken from each of the formulated diets and from the Control diet.

The samples were analysed for concentration and homogeneity using the method validated under Inveresk Project No. 363930 (Method No. 6393). Stability over 14 days was demonstrated in that project.

OBSERVATIONS

Clinical Observations

All the animals were examined for reaction to treatment each day. The nature, onset, duration and intensity of any signs were recorded.

In addition to the above, all the animals were checked for viability at the beginning of each day and again as late as practical in each day.

Body Weight

Weights of F_0 animals were recorded one week prior to the first day of test material administration, then weekly thereafter until the start of the mating period. Males continued weekly weighing until termination. Weights for females were also recorded on Day 0 of gestation (the day of detection of a positive mating sign) and Days 7, 14 and 20 of gestation, then on Days 1, 7, 14 and 21 of lactation (where the day of birth of the litter was designated Day 0 of lactation).

Pre-weaning F_1 and F_2 pups were weighed *en masse* (sexes separate) on Days 1, 4, 7 and 14 of lactation. The pups were weighed individually on Day 21 of lactation, and the total litter weight was also recorded.

Post-weaning F_1 animals were weighed weekly from a convenient day when the animals were approximately 4 weeks old until the start of their mating period. Thereafter, they followed the same regime of weighing as described for F_0 animals.

Post-weaning F_2 animals were weighed weekly until sacrifice.

Food Consumption

Food consumption was recorded weekly for each cage of F_0 animals, commencing one week prior to commencement of treatment. Food consumption monitoring was suspended during the mating period and then, for males, recommenced as before. For mated females, consumption for individual animals was measured over the following period:

Days 0-7, 7-14 and 14-20 of gestation, and Days 0-7, 7-14 and 14-21 of lactation

For F_1 and F_2 animals, consumption was recorded weekly from a convenient day, when animals were approximately 4 weeks old. Thereafter, food consumption was recorded following the same regime as the F_0 animals.

Mating Procedure

Animals were paired on a one male to one female basis, sibling matings and other closely related pairings being avoided. Each female was transferred to the cage of its designated co-group male near the end of the work day, where it remained until mating was detected or 7 nights had elapsed. A vaginal lavage was examined early each morning, commencing on the morning of pairing, until a mating sign was detected; the day of detection of sperm in the lavage, or of a copulatory plug *in situ* was considered to be Day 0 of gestation. The state of the oestrous cycle in each lavage was recorded to assist with interpretation of mating performance, and to provide an indication of any disturbance of the oestrous cycle.

Each female was left with its first designated male for a maximum of 7 nights. If no mating sign was detected during that time, a rest period of 2 days was allowed before the female was placed with a second co-group male, which had already mated. After 14 nights with the second male, if no mating sign was detected, attempts to breed from the female ceased and she was transferred to an individual, solid bottomed cage.

Observations on Females and Litters During the Lactation Period

The females were allowed to litter normally. The day on which parturition commenced was designated Day 0 of lactation. The duration of gestation in days was calculated. The number of live pups born and the number found dead in each litter was recorded as soon as possible after completion of parturition.

The live pups were sexed, counted, examined for the presence of milk in the stomach and for any externally visible abnormalities daily up to Day 4 of lactation; they were counted and examined for abnormalities again on Days 7, 14 and 21. The pups were weighed as previously specified, on Days 1, 4, 7 and 21 of lactation. Where practicable, any pups found dead or killed during lactation were sexed as above.

Any deficiencies in maternal care were recorded: points looked for included inadequate construction and cleaning of the nest, pups left scattered and cold, physical abuse of pups, or apparently inadequate lactation or feeding.

The following reproductive indices were calculated:

For each group:

$$\text{Fertility Index} = \frac{\text{Number of pregnant females / siring males}}{\text{Number Paired}}$$

$$\text{Gestation Index} = \frac{\text{Number bearing live pups}}{\text{Number Pregnant}}$$

For each litter and group:

$$\text{Birth Index} = \frac{\text{Total number of pups born (live and dead)}}{\text{Number of implantation scars}}$$

$$\text{Live Birth Index} = \frac{\text{Number of pups live on Day 0 of lactation}}{\text{Total number born (live and dead)}}$$

$$\text{Viability Index} = \frac{\text{Number of pups live on Day 4 of lactation}}{\text{Number live on Day 0}}$$

$$\text{Lactation Index} = \frac{\text{Number of pups live on Day 21 of lactation}}{\text{Number live on Day 4}}$$

$$\text{Overall Survival Index} = \frac{\text{Number of pups live on Day 21 of lactation}}{\text{Total number of pups born (live or dead)}}$$

Selection of F_1 Pups for Mating to Produce the F_2 Generation and F_2 Pups for Post-Weaning Assessment

On Day 21 of lactation, 24 male and 24 female F_1 pups were selected per treatment group. Nominally, one male and one female were selected from each of 24 litters.

On Days 21-24 of lactation, one male and one female F_2 pup per litter were selected. By oversight, occasional additional animals were selected, and these were treated as spares; this slight protocol deviation did not compromise the study.

Within each litter, the median'th weight pup of each sex was selected; where a second pup of that sex was selected, the next highest pup by weight was selected. The selected animals were then individually identified by ear marking and remained with their litter mates and mother until weaning.

Additionally, 2 male and 2 female F_1 pups per group were selected as spares against the contingency of occasional litters failing to reach weaning, or to replace animals that died during the immediate post-weaning period. These spares were not needed, and were killed without necropsy.

F_1 and F_2 Weaning

For the selected pups, this was effected on Day 24 of lactation, when they were removed from their mother and re-housed 2 per grid bottomed cage, sexes on separate racks. The cages were ordered according to a newly generated random sequence of treatment groups, which applied to both male and female cage arrays.

Pups that were not selected remained with their mother until termination.

Sexual Maturation of F_1 and F_2 Pups

Commencing at 28 days of age all selected females were examined daily for vaginal opening. The day on which the vagina became open was recorded along with that day's body weight.

Males were examined daily for balano-preputial separation from 35 days of age. The day on which separation occurred and the body weight was recorded.

TERMINAL STUDIES

The animals were killed by carbon dioxide asphyxiation.

F_0, F_1 and F_2 Adults

These animals were subjected to a necropsy, consisting of an external examination, followed by macroscopic examination of the tissues and organs of the cranial, thoracic and abdominal cavities. Any gross lesions were described and representative samples taken and fixed in neutral buffered 10% formalin. The following organs were weighed (where indicated) and fixed:

Ovaries
Uterus, cervix and vagina
Testes (weighed individually), and fixed in Bouin's fluid
Epididymides (weighed individually)
Seminal vesicle, coagulating gland (weighed)
Prostate gland (weighed)
Pituitary gland
Liver (weighed)
Kidneys (weighed individually)

The female reproductive tract in F_0 and F_1 animals was examined for signs of pregnancy and the number of visible implantation sites was recorded.

All tissues were fixed in 10% buffered neutral formalin.

Carcasses were discarded following these procedures.

F_1 and F_2 Pups (Pre-weaning)

Offspring found dead or killed before Day 14 of lactation were sexed, examined for externally visible abnormalities and for the presence of milk in the stomach. Any abnormal pups were necropsied.

Offspring dying on or after Day 14 were subjected to a gross necropsy, in which the cranial, thoracic and abdominal contents were examined macroscopically; any findings were recorded and abnormal tissues sampled, as appropriate.

F_1 and F_2 Pups (At Weaning)

From each litter, 2 male and 2 female pups were necropsied.

The necropsy consisted of an external examination, followed by macroscopic examination of the tissues and organs of the cranial, thoracic and abdominal cavities. Any gross lesions were described and representative samples taken and fixed in neutral buffered 10% formalin.

From one male in each litter, the testes were weighed individually and preserved as described for adult males. The body weight of these pups was recorded at necropsy.

Carcasses were discarded following these procedures.

The remaining pups (except F_1 weanlings selected for rearing to produce the next generation and F_2 weanlings selected for post weaning assessment generation) were killed after external examination and the carcasses discarded without necropsy.

Histology Evaluation

Histological examination was conducted on the testes and epididymides of F_0 and F_1 rats for qualitative and quantitative investigation of any effects on spermatogenesis. The High dose and Control specimens were processed.

Representative transverse sections, 4-6 µm thick, were cut from each testis and stained by the Periodic Acid Schiff and Haematoxylin (PAS-H) method. A total of 100 tubule cross-sections (50 from each testis, where possible) were 'staged' according to the method described by Russell *et al*, 1990 and the following evaluations applied:

Frequency of the various stages.

Evaluation of each stage for damage or absence of component cell types.

Tubule diameter for 20 cross-sections per animal, where possible.

The ovaries, uterus, cervix, vagina, epididymides, seminal vesicles and coagulating gland, pituitary and any macroscopically abnormal tissues from all F_0 and F_1 Control and High dose animals were processed and 4-6 µm thick sections were stained with haematoxylin and eosin (H&E) and evaluated by light microscopy.

Statistical Analysis of Results

Where considered appropriate to assist with interpretation, statistical analysis was applied to determine the statistical significance of differences from Control. Organ weight data were analysed by analysis of variance, and by analysis of covariance using the terminal body weight as the single covariate (Snedecor and Cochran, 1980). Pairwise comparisons between each treatment level and Control were performed using Fisher's F-protected Least Significant Differences.

RESULTS

Analysis of Formulated Diets (Appendix 5)

The analysed concentrations of the formulated diets prepared for the first week of dosing, were low (up to 17.6% lower than the nominal). The method of analysis was then amended, and a repeat analysis performed two weeks later. The analysed concentration for these formulated diets, and those sampled throughout the remainder of the study, were within ± 7% of the nominal. It was therefore considered that all diets had been correctly formulated, and the apparently low concentrations in the initial formulations reflected the limitations of the initial analytical method.

Clinical Observations (Tables 1,2 and Appendices 6-9)

There were no clinical findings observed which were considered to be related to treatment.

The findings in F_2 animals comprised of one incidence of scabbing and one incidence of swollen tail (findings for F_2 animals have not been tabulated).

One F_0 animal (Animal 150♀) at 1000 p.p.m. was found dead in late lactation. There were no findings to indicate any effect of treatment.

Body Weight Performance (Tables 3-10 and Appendices 10-17)

At 10000 p.p.m. weight gain of males in the F_0 and F_1 generations, and also in the retained F_2 generation, was lower than Control throughout the treatment period. There were no obvious effects on body weights of females at this level; marginal differences in performance during lactation were considered too small to be attributable to treatment.

There were no effects of treatment on weight gain at the lower dose levels.

Food Consumption (Tables 11-18 and Appendices 18-25)

At 10000 p.p.m. food consumption of males in the F_0 and F_1 generations was slightly lower than that of the Controls. A slight reduction in food consumption was observed in F_0 females over Days 7-21 of lactation and in F_1 females throughout lactation. There was no effect on food consumption in females during the pre mating period. Differences in the retained F_2 generation were considered too small to be attributable to treatment.

There were no effects of treatment on food consumption in animals treated at the lower levels.

Achieved Dosages (Tables 19-22)

At all times the ratio between achieved dosages was essentially similar to the ratio of the dietary concentrations.

As expected there was a steady decrease in achieved dosages with time over the treatment period for the males and during the pre mating period for the females. During the gestation and lactation periods the values were generally increased and by the end of lactation values were up to 3 times higher than those during the pre mating period.

Mating Performance, Fertility Indices and Duration of Gestation (Tables 23-26 and Appendices 26, 31)

There were no obvious effects of treatment on mating performance, fertility indices or the duration of gestation.

Litter Size and Survival (Tables 25-28 and Appendices 26, 27, 31, 32)

The mean numbers of implant sites were similar in all groups.

At 10000 p.p.m. there was a slight increase in the number of F_0 and F_1 animals losing more than 1 pup during Days 4 to 21 of lactation, with the corresponding slight reduction in litter size over that period.

At the lower levels, litter size and survival were similar to Control.

Litter and Pup Weights (Tables 29, 30 and Appendices 28, 29, 33, 34)

At 10000 p.p.m. litter and pup weight in both generations were lower than Control.

Pup weights at 3000 p.p.m. were similar to Control, but litter weights were slightly lower, reflecting an incidentally lower litter size.

At 1000 p.p.m. litter weight and pup weight were essentially similar to Control.

Assessment of Sexual Maturity (Tables 31, 32 and Appendices 36-39)

At 10000 p.p.m. , the mean age of preputial separation was marginally greater than Control, although body weights at the time of separation were similar. Considering the 2 generations together, the mean age at separation at the lower levels was similar to Control.

In F_1 animals at 3000 and 10000 p.p.m. vaginal opening occurred slightly later than that in Controls; body weight was marginally higher than that of the Controls. In the F_2 animals there were no differences in the age of vaginal opening.

Organ Weights (Tables 33-48 and Appendices 40-47)

Testes

In F_0, F_1 and F_2 adults, mean absolute testes weights were similar in all groups; following covariance analysis, the adjusted weight of F_1 males at 10000 p.p.m. 610P was slightly greater than Control with the difference attaining statistical significance. Among weanlings, the testes weights at 10000 p.p.m. were slightly lower than Control, with the values for F_1 weanlings attaining statistical significance.

Seminal Vesicles

Mean seminal vesicles weights were reduced at 10000 p.p.m. , with absolute values consistently significant, and adjusted values significant for F_1 and F_2 adults. In the F_2 adults, seminal vesicles weights at 3000 p.p.m. were also significantly lower. At 1000 p.p.m. seminal vesicles weights of F_2 adults were marginally lower than Control, but the differences were not statistically significant and were considered to be probably incidental in the absence of similar effects in the other generations.

Prostate

Mean prostate weights of F_1 adults at 10000 p.p.m. were significantly lower than Control.

Epididymides

The mean epididymides weight of F_0 adults at 10000 p.p.m. was slightly lower than Control, with the difference attaining statistical significance; however, this difference was no longer significant after adjustment for body weight and in the

absence of similar findings in other generations the apparent difference was considered to reflect the lower body weights of these animals.

Liver

Mean liver weights of females in all generations at 10000 p.p.m. and of F_0 and F_1 females at 3000 p.p.m. were significantly increased. At 1000 p.p.m. the liver weight of F_1 females was significantly increased, and for F_0 females the absolute liver weight was also increased, although the statistical significance was no longer apparent after adjustment for body weight.

Among males, assessment of effects on liver weight was complicated by body weight effects: after covariance adjustment, liver weights of F_0 and F_2 males at 3000 and 10000 p.p.m. were increased, but weights for F_1 animals were similar to Control. In all generations, liver weights at 1000 p.p.m. were similar to Control.

Kidneys

After adjustment for body weight, mean kidney weights of F_0 and F_1 females at 3000 and 10000 p.p.m. were greater than Control, and there was also a slight increase among F_1 females at 1000 p.p.m.

Among males, kidney weights at 3000 and 10000 p.p.m. in the F_1 generation were increased, but similar increases were not seen in the other generations. Apparent reductions in kidney weights, which were no longer present after adjustment for body weight, were considered to reflect the lower body weights.

Necropsy Findings (Tables 49, 51 and 53 and Appendices 48-50)

Necropsy findings in the majority of F_0 , F_1 and F_2 males at 10000 p.p.m. included discoloured, enlarged and pale liver with prominent lobulation and/ or pale/ dark focus.

Pale liver foci were also observed for occasional males at 3000 p.p.m. and for occasional females at 10000 and 3000 p.p.m.

The other necropsy findings were considered to be incidental.

Histology Findings (Tables 50 and 52 and Appendices 48, 49)

Histology at 10000 p.p.m. revealed numerous findings affecting the liver in the majority F_0 and F_1 males; these comprised of generalised cellular change, basophilic foci(us), vacuolated focus, eosinophilic cell focus, clear cell focus, bile duct hyperplasia and Kupffer-cell pigmentation.

The remaining findings were considered not to be related to treatment.

Assessment of Tubule Staging and Diameter (Table 54 and Appendices 50, 51)

Values for tubular staging and diameter in the High dose group were similar to Control values.

DISCUSSION AND CONCLUSION

Toxicity in adult male animals dosed at 10000 p.p.m. was manifest by reductions in weight gain in all generations and by reduced food consumption in the F_0 and F_1 generations. There was some reduction in food consumption during lactation among females at 10000 p.p.m.

There were no obvious effects of treatment on the mating performance, fertility indices or duration of gestation.

At 10000 p.p.m. 610 P litter survival was slightly decreased across Days 4 to 21, and there were slight decreases in pup and litter weights. Pup survival, and litter and pup weights at the lower levels were similar to Control.

Taking the 2 generations together, it was considered that there was a marginal delay in sexual maturity at 10000 p.p.m., but that sexual maturity at the lower levels was attained at a similar age to that of Controls.

At 10000 p.p.m., mean absolute testes weights among adults were similar to Control; adjusted weights for F_1 adults were slightly increased, while weights for weanlings at this level were slightly decreased. The weights of seminal vesicles in adults at 10000 p.p.m. were reduced, and this reduction extended to F_2 adults at 3000 p.p.m. Mean prostate weight was reduced among F_1 adults at 10000 p.p.m.

There were no effects noted on the tubule diameter or distribution of tubule stages noted in the testes.

Mean kidney weights of females at 3000 and 10000 p.p.m. were increased in the F_0 and F_1 generations, and there was a slight increase among F_1 females at 1000 p.p.m. Kidney weights of F_1 males at 3000 and 10000 p.p.m. were also increased.

Liver weights of females at 3000 and 10000 p.p.m. were increased; liver weights of F_0 and F_2 males at these levels were also increased, but weights for F_1 males were similar to Control. Liver weights of F_1 females at 1000 p.p.m. were increased. At necropsy, most adult males at 10000 p.p.m. had necropsy findings in the liver, including discoloured, enlarged and pale liver with prominent lobulation and/or pale/dark focus. Pale liver foci were also observed for occasional males at 3000 p.p.m. and for occasional females at 10000 p.p.m. Most F_0 and F_1 males at 10000 p.p.m. had histological findings in the liver, including generalised cellular change, basophilic foci(us), vacuolated focus, eosinophilic cell focus, clear cell focus, bile duct hyperplasia and Kupffer-cell pigmentation.

In this study, the 'reproductive' effects were considered to be the reduced pup survival and weights, and marginal delay in sexual maturity at 10000 p.p.m. Effects on the reproductive organs, liver and kidney were essentially similar in all generations and were therefore not classed as specific reproductive effects.

In conclusion, therefore, the no effect level for reproductive effects was considered to be 3000 p.p.m. It was not possible to identify a no effect level in this study, although effects at 1000 p.p.m. were confined to increased liver and kidney weights among F_1 females.

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TABLE 1

610 P
Two Generation Reproduction Study in Rats
F_0 Generation
Group Incidence of Clinical Observations - Males and Females

Observation/Finding	Group/Dose Level (p.p.m. 610 P)			
	1 (0)	2 (1000)	3 (3000)	4 (10000)
Total number examined	56	56	56	56
Hairloss	2	4	1	0
Encrustations	1	4	2	0
Staining of coat	2	13	10	8
Unkempt coat	0	0	0	2
Agitated behaviour	1	2	0	0
Left eye dark	0	1	0	0
Red ears	0	0	1	0
Animal limping with red and/or swollen feet	0	0	0	1
Piloerection	1	1	0	1
Teeth overgrown/ small/ cut/broken or missing	0	0	1	2
Lump in ventral thoracic or ventral abdominal regions	0	1	1	2
Subdued behaviour	1	0	0	0
Skin cold to touch	1	0	0	0
Hunched appearance	1	0	0	1
Animal found dead	0	1	0	0

TABLE 2

610 P
Two Generation Reproduction Study in Rats
F_1 Generation
Group Incidence of Clinical Observations - Males and Females

Observation/Finding	Group/Dose Level (p.p.m. 610 P)			
	1 (0)	2 (1000)	3 (3000)	4 (10000)
Total number examined	56	56	56	56
Soft and/ or yellow faeces	1	0	0	0
Damaged ear with/without scabbing	1	0	0	1
Teeth misaligned/ overgrown/ broken or white	3	0	5	0
Hairloss	5	2	3	5
Encrustations	0	2	1	0
Staining of coat	0	4	4	8
Staining of tray paper	0	1	0	0
Red discharge from eye	0	0	1	0
Agitated behaviour	2	0	1	1
Animal vocalised whilst being held	1	0	0	0
Piloerection	0	0	2	0
Hunched appearance	1	0	1	0
Ears red	0	1	1	1

TABLE 3

610 P
Two Generation Reproduction Study in Rats
F_0 Generation Males
Group Mean Body Weight (g) ± Standard Deviation

Week of Treatment	Group/Dose Level (p.p.m. 610 P)			
	1 (0)	2 (1000)	3 (3000)	4 (10000)
Pretrial	155 ± 15	152 ± 15	150 ± 13	148 ± 16
0	222 ± 19	218 ± 19	214 ± 15	213 ± 19
1	280 ± 20	275 ± 23	266 ± 17	260 ± 24
2	336 ± 23	331 ± 25	321 ± 19	306 ± 29
3	372 ± 28	369 ± 29	359 ± 23	335 ± 33
4	408 ± 31	403 ± 33	392 ± 27	359 ± 39
5	435 ± 34	430 ± 39	417 ± 30	376 ± 43
6	453 ± 37	447 ± 44	433 ± 33	385 ± 47
7	476 ± 38	469 ± 47	457 ± 33	405 ± 49
8	495 ± 42	490 ± 51	477 ± 37	421 ± 54
9	515 ± 43	512 ± 54	494 ± 37	435 ± 54
10	521 ± 44	522 ± 56	504 ± 38	441 ± 53
11	534 ± 43	534 ± 58	515 ± 38	452 ± 52
12	539 ± 46	541 ± 60	522 ± 36	456 ± 53
13	554 ± 44	555 ± 64	534 ± 38	470 ± 53
14	560 ± 47	562 ± 62	540 ± 39	475 ± 56
15	573 ± 47	579 ± 67	554 ± 39	486 ± 57
16	588 ± 47	589 ± 68	565 ± 39	497 ± 58
Weight Gain Weeks 0-16	366 ± 41	371 ± 61	351 ± 36	284 ± 48
% of Control	-	101	96	78

TABLE 4

610 P
Two Generation Reproduction Study in Rats
F_0 Generation Females
Group Mean Body Weight (g) Prior to Mating ± Standard Deviation

Week of Treatment	Group/Dose Level (p.p.m 610 P)			
	1 (0)	2 (1000)	3 (3000)	4 (10000)
Pretrial	118 ± 14	120 ± 13	120 ± 16	120 ± 14
0	154 ± 18	158 ± 15	158 ± 19	158 ± 14
1	180 ± 21	185 ± 18	187 ± 22	185 ± 16
2	203 ± 24	209 ± 20	210 ± 24	209 ± 19
3	223 ± 29	230 ± 21	232 ± 24	230 ± 17
4	241 ± 31	249 ± 23	250 ± 27	248 ± 20
5	255 ± 32	263 ± 25	263 ± 29	262 ± 21
6	265 ± 33	275 ± 27	274 ± 29	275 ± 22
7	275 ± 36	284 ± 26	284 ± 30	283 ± 23
8	284 ± 40	297 ± 27	296 ± 31	292 ± 22
9	296 ± 38	307 ± 30	303 ± 33	302 ± 24
10	300 ± 39	309 ± 31	307 ± 33	303 ± 25
Weight Gain Weeks 0-10	146 ± 25	151 ± 21	149 ± 20	145 ± 18
% of Control	-	103	102	99

TABLE 5

610 P
Two Generation Reproduction Study in Rats
F_0 Generation Females
Group Mean Body Weight (g) During Gestation and Lactation ± Standard Deviation

	Group/Dose Level (p.p.m. 610 P)			
	1 (0)	2 (1000)	3 (3000)	4 (10000)
Day of Gestation[a]				
0	300 ± 40	310 ± 30	303 ± 27	310 ± 31
7	329 ± 41	338 ± 30	332 ± 28	332 ± 24
14	364 ± 44	371 ± 31	364 ± 30	362 ± 24
20	442 ± 51	446 ± 37	439 ± 38	447 ± 27
Weight Gain Days 0-20	142 ± 18	137 ± 20	136 ± 21	137 ± 21
% of Control	-	96	96	96
Day of Lactation[b]				
1	313 ± 41	330 ± 32	324 ± 26	326 ± 26
7	353 ± 37	368 ± 29	360 ± 29	357 ± 21
14	358 ± 39	376 ± 36	368 ± 30	347 ± 27
21	333 ± 35	348 ± 29	347 ± 27	325 ± 33

a = Pregnant animals only
b = Animals rearing young to Day 21 only

TABLE 6

610 P
Two Generation Reproduction Study in Rats
F_1 Generation Males
Group Mean Body Weight (g) ± Standard Deviation

Week of Age (Nominal)	Group/Dose Level (p.p.m. 610 P)			
	1 (0)	2 (1000)	3 (3000)	4 (10000)
4	106 ± 13	107 ± 18	107 ± 17	106 ± 16
5	167 ± 18	166 ± 24	166 ± 20	166 ± 21
6	225 ± 21	226 ± 29	226 ± 24	223 ± 24
7	283 ± 23	284 ± 33	284 ± 26	275 ± 27
8	332 ± 24	334 ± 34	334 ± 28	316 ± 28
9	367 ± 28	369 ± 36	367 ± 31	343 ± 32
10	394 ± 33	398 ± 39	396 ± 33	363 ± 38
11	421 ± 37	421 ± 40	418 ± 40	384 ± 41
12	436 ± 39	436 ± 41	432 ± 42	395 ± 40
13	453 ± 45	451 ± 41	449 ± 43	404 ± 42
14	470 ± 45	467 ± 42	469 ± 45	417 ± 45
15	484 ± 44	479 ± 44	482 ± 46	424 ± 47
16	497 ± 47	491 ± 46	497 ± 44	436 ± 45
17	510 ± 51	508 ± 47	512 ± 43	449 ± 44
18	523 ± 53	520 ± 45	527 ± 48	460 ± 46
19	535 ± 53	527 ± 47	536 ± 48	468 ± 49
20	546 ± 52	536 ± 49	548 ± 52	474 ± 50
21	559 ± 54	546 ± 49	559 ± 53	484 ± 50
22	570 ± 54	559 ± 50	569 ± 55	492 ± 48
Weight Gain Weeks 4-22	464 ± 51	450 ± 43	462 ± 51	385 ± 47
% of Control	-	97	100	83

TABLE 7

610 P
Two Generation Reproduction Study in Rats
F_1 Generation Females
Group Mean Body Weight (g) Prior to Mating ± Standard Deviation

Week of Age (Nominal)	Group/Dose Level (p.p.m. 610 P)			
	1 (0)	2 (1000)	3 (3000)	4 (10000)
4	95 ± 9	97 ± 13	97 ± 13	93 ± 13
5	138 ± 12	137 ± 15	137 ± 15	136 ± 13
6	169 ± 14	167 ± 16	168 ± 16	169 ± 14
7	195 ± 18	191 ± 16	193 ± 18	195 ± 16
8	218 ± 21	215 ± 18	216 ± 19	217 ± 16
9	237 ± 24	233 ± 20	235 ± 21	236 ± 17
10	252 ± 26	247 ± 19	249 ± 22	248 ± 18
11	264 ± 28	258 ± 22	262 ± 23	262 ± 19
12	272 ± 30	267 ± 21	271 ± 24	272 ± 20
13	281 ± 29	274 ± 23	279 ± 24	276 ± 20
14	287 ± 30	282 ± 24	286 ± 26	281 ± 22
15	294 ± 32	287 ± 22	290 ± 27	285 ± 22
Weight Gain Weeks 4-15	199 ± 29	190 ± 18	194 ± 22	191 ± 24
% of Control	-	95	97	96

TABLE 8

610 P
Two Generation Reproduction Study in Rats
F_1 Generation Females
Group Mean Body Weight (g) During Gestation and Lactation ± Standard Deviation

	Group/Dose Level (p.p.m. 610 P)			
	1 (0)	2 (1000)	3 (3000)	4 (10000)
Day of Gestation[a]				
0	299 ± 30	294 ± 27	293 ± 27	287 ± 23
7	328 ± 34	323 ± 29	323 ± 28	310 ± 23
14	362 ± 36	354 ± 29	353 ± 31	337 ± 24
20	443 ± 42	437 ± 36	435 ± 36	418 ± 35
Weight Gain Days 0-20	143 ± 21	143 ± 16	142 ± 18	130 ± 23
% of Control	-	100	99	91
Day of Lactation[b]				
1	319 ± 40	315 ± 37	313 ± 37	300 ± 32
7	359 ± 33	354 ± 41	353 ± 31	330 ± 23
14	365 ± 33	364 ± 31	360 ± 33	329 ± 21
21	347 ± 29	347 ± 32	350 ± 25	318 ± 22

a = Pregnant animals only
b = Animals rearing young to Day 21 only

TABLE 9

610 P
Two Generation Reproduction Study in Rats
F_2 Generation Males
Group Mean Body Weight (g) ± Standard Deviation

Week of Age (nominal)	Group/Dose Level (p.p.m. 610 P)			
	1 (0)	2 (1000)	3 (3000)	4 (10000)
4	114 ± 14	112 ± 13	112 ± 18	106 ± 15
5	171 ± 19	168 ± 15	168 ± 24	161 ± 20
6	233 ± 23	225 ± 18	230 ± 27	219 ± 23

TABLE 10

610 P
Two Generation Reproduction Study in Rats
F_2 Generation Females
Group Mean Body Weight (g) ± Standard Deviation

Week of Age (nominal)	Group/Dose Level (p.p.m. 610 P)			
	1 (0)	2 (1000)	3 (3000)	4 (10000)
4	101 ± 12	100 ± 11	98 ± 14	95 ± 13
5	141 ± 15	137 ± 12	141 ± 16	137 ± 15
6	167 ± 16	164 ± 14	172 ± 16	168 ± 17

TABLE 11

610 P
Two Generation Reproduction Study in Rats
F_0 Generation Males
Group Mean Food Consumption ($g.rat^{-1}.day^{-1}$)

Week of Treatment	Group/Dose Level (p.p.m. 610 P)			
	1 (0)	2 (1000)	3 (3000)	4 (10000)
Pretrial	25.3	24.9	24.7	24.4
1	27.1	27.1	26.2	26.3
2	31.8	32.0	31.3	30.7
3	31.8	32.1	31.4	29.7
4	32.2	31.9	30.9	28.7
5	32.0	31.8	31.0	28.4
6	31.8	31.3	30.2	27.5
7	31.8	31.2	31.8	29.6
8	31.5	32.1	30.9	28.9
9	31.5	32.0	30.7	28.3
10	31.6	33.0	31.7	29.3
12	29.8	30.1	29.6	27.5
13	32.0	32.2	30.8	29.6
14	32.3	32.8	31.5	29.1
15	31.8	32.5	31.3	29.1
16	32.6	32.6	31.6	29.8

TABLE 12

610 P
Two Generation Reproduction Study in Rats
F_0 Generation Females
Group Mean Food Consumption Prior to Mating ($g.rat^{-1}.day^{-1}$)

Week of Treatment	Group/Dose Level (p.p.m. 610 P)			
	1 (0)	2 (1000)	3 (3000)	4 (10000)
Pretrial	19.2	19.3	19.5	19.2
1	19.5	19.9	20.5	20.0
2	21.1	22.0	21.9	21.8
3	22.4	22.9	22.8	23.2
4	22.6	23.3	23.3	23.5
5	23.0	23.7	23.7	23.7
6	23.0	23.6	23.6	23.9
7	23.3	23.8	23.9	24.2
8	23.0	23.9	23.9	23.9
9	22.9	23.3	23.6	23.7
10	21.8	22.4	22.5	22.4

TABLE 13

610 P
Two Generation Reproduction Study in Rats
F_0 Generation Females
Group Mean Food Consumption During Gestation and Lactation ($g.rat^{-1}.day^{-1}$)

	Group/Dose Level (p.p.m. 610 P)			
	1 (0)	2 (1000)	3 (3000)	4 (10000)
Day of Gestation[a]				
0-7	27.1	27.8	28.1	28.1
7-14	30.4	30.3	30.5	31.4
14-20	32.0	33.4	32.8	36.1
Day of Lactation[b]				
0-7	44.5	47.1	46.4	48.6
7-14	76.4	75.3	76.1	69.7
14-21	87.7	87.6	85.4	76.6

a = Pregnant animals only
b = Animals rearing young to Day 21 only

TABLE 14

610 P
Two Generation Reproduction Study in Rats
F_1 Generation Males
Group Mean Food Consumption ($g.rat^{-1}.day^{-1}$)

Week of Age (Nominal)	Group/Dose Level (p.p.m. 610 P)			
	1 (0)	2 (1000)	3 (3000)	4 (10000)
5	20.8	20.8	21.2	21.1
6	26.1	26.2	26.1	25.9
7	29.7	29.8	29.9	29.5
8	32.3	32.6	32.3	31.5
9	32.3	32.4	32.1	30.6
10	32.3	32.9	32.3	30.6
11	31.8	31.6	31.1	29.2
12	31.5	30.6	30.5	28.7
13	32.3	31.6	32.0	30.6
14	31.6	31.2	31.3	29.9
18	30.3	29.5	30.3	28.0
19	31.4	30.4	30.9	28.8
20	31.5	30.7	31.6	29.1
21	31.3	31.1	31.7	28.8
22	31.1	31.3	31.4	28.8

TABLE 15

610 P
Two Generation Reproduction Study in Rats
F_1 Generation Females
Group Mean Food Consumption Prior to Mating ($g.rat^{-1}.day^{-1}$)

Week of Age (Nominal)	Group/Dose Level (p.p.m. 610 P)			
	1 (0)	2 (1000)	3 (3000)	4 (10000)
5	18.6	18.2	18.3	18.2
6	21.0	19.5	20.5	20.8
7	22.3	21.2	21.6	21.4
8	23.6	22.6	23.2	22.7
9	23.9	23.5	23.0	23.1
10	24.4	23.8	23.8	24.0
11	24.4	24.0	23.6	24.0
12	24.3	24.0	23.8	24.4
13	24.1	24.0	23.7	23.7
14	23.8	24.3	23.9	24.1

TABLE 16

610 P
Two Generation Reproduction Study in Rats
F_1 Generation Females
Group Mean Food Consumption During Gestation and Lactation ($g.rat^{-1}.day^{-1}$)

	Group/Dose Level (p.p.m. 610 P)			
	1 (0)	2 (1000)	3 (3000)	4 (10000)
Day of Gestation[a]				
0-7	27.8	27.6	28.1	27.2
7-14	29.5	28.9	29.5	28.4
14-20	31.1	30.8	31.1	31.3
Day of Lactation[b]				
0-7	45.7	48.1	46.7	36.1
7-14	75.4	77.6	75.4	55.3
14-21	87.9	90.0	91.8	62.6

a = Pregnant animals only
b = Animals rearing young to Day 21 only

TABLE 17

610 P
Two Generation Reproduction Study in Rats
F_2 Generation Males
Group Mean Food Consumption ($g.rat^{-1}.day^{-1}$)

Week of Age (nominal)	Group/Dose Level (p.p.m. 610 P)			
	1 (0)	2 (1000)	3 (3000)	4 (10000)
5	21.8	20.1	21.1	20.5
6	27.1	25.2	26.0	25.7

TABLE 18

610 P
Two Generation Reproduction Study in Rats
F_2 Generation Females
Group Mean Food Consumption ($g.rat^{-1}.day^{-1}$)

Week of Age (nominal)	Group/Dose Level (p.p.m. 610 P)			
	1 (0)	2 (1000)	3 (3000)	4 (10000)
5	19.2	17.9	19.5	18.9
6	21.1	20.0	21.3	20.9

TABLE 19

610 P
Two Generation Reproduction Study in Rats
F_0 Generation Males
Group Mean Achieved Dosages of Test Material (mg 610 P.kg^{-1}.day^{-1})

Week of Treatment	Group/Dose Level (p.p.m. 610 P)		
	2 (1000)	3 (3000)	4 (10000)
1	147	432	1458
2	130	391	1300
3	106	320	1049
4	91	273	895
5	82	248	818
6	75	224	749
7	71	224	777
8	70	208	730
9	67	197	686
10	66	196	683
12	57	174	617
13	60	178	652
14	60	179	629
15	58	175	616
16	57	173	620

TABLE 20

610 P
Two Generation Reproduction Study in Rats
F_0 Generation Females
Group Mean Achieved Dosages of Test Material (mg 610 P.kg^{-1}.day^{-1})

Week of Treatment	Group/Dose Level (p.p.m. 610 P)		
	2 (1000)	3 (3000)	4 (10000)
1	143	442	1440
2	128	381	1273
3	116	344	1179
4	106	316	1072
5	99	295	993
6	92	276	935
7	89	267	901
8	85	257	857
9	80	244	824
10	74	226	754
Week of Gestation			
1	82	256	779
2	82	253	839
3	79	245	860
Week of Lactation[a]			
1	135	407	1423
2	202	627	1980
3	242	650	2280

a = These calculations assume that all the diet was eaten by the dam

TABLE 21

610 P
Two Generation Reproduction Study in Rats
F_1 Generation Males
Group Mean Achieved Dosages of Test Material (mg 610 P.kg^{-1}.day^{-1})

Week of Age (Nominal)	Group/Dose Level (p.p.m. 610 P)		
	2 (1000)	3 (3000)	4 (10000)
5	153	465	1546
6	134	400	1331
7	117	352	1187
8	105	313	1064
9	92	275	930
10	86	254	867
11	77	229	783
12	71	215	736
13	71	218	766
14	68	205	728
18	57	175	616
19	58	174	621
20	58	174	618
21	57	172	601
22	57	167	591

TABLE 22

610 P
Two Generation Reproduction Study in Rats
F_1 Generation Females
Group Mean Achieved Dosages of Test Material (mg 610 P.kg^{-1}.day^{-1})

Week of Age (Nominal)	Group/Dose Level (p.p.m. 610 P)		
	2 (1000)	3 (3000)	4 (10000)
5	173	469	2666
6	147	403	1360
7	129	358	1988
8	119	340	1100
9	110	305	1018
10	103	295	990
11	98	277	939
12	93	268	914
13	90	258	866
14	88	253	863
Week of Gestation			
1	78	250	714
2	74	239	689
3	71	237	711
Week of Lactation[a]			
1	144	421	1146
2	316	635	1678
3	253	776	1935

a = These calculations assume that all food was eaten by the dam

TABLE 23

610 P
Two Generation Reproduction Study in Rats
F_0 Generation
Mating Performance and Fertility Indices

Number of Nights to Positive Mating Sign	Group/Dose Level (p.p.m. 610 P)			
	1 (0)	2 (1000)	3 (3000)	4 (10000)
	Number of Animals (Number of these not becoming pregnant)			
1	6	4 (1)	9	8
2	6	5	6 (1)	11 (1)
3	10	10	5	5
4	5	7 (1)	7	3
7	0	0	1	0
8-14	1	1	0	1
15-21	0	1	0	0
Median number of nights to positive mating sign	3	3	2	2
Number passing one oestrus	0	0	1	0
Number passing 2 oestruses	1	1	0	0
Number of males paired	28	28	28	28
Number of siring males	27	24	27	26
Male Fertility Index (%)	96	86	96	93
Number of females paired	28	28	28	28
Number pregnant	28	26	27	27
Female Fertility Index (%)	100	93	96	96

TABLE 24

610 P
Two Generation Reproduction Study in Rats
F_1 Generation
Mating Performance and Fertility Indices

Number of Nights to Positive Mating Sign	Group/Dose Level (p.p.m. 610 P)			
	1 (0)	2 (1000)	3 (3000)	4 (10000)
	Number of Animals (Number of these not becoming pregnant)			
1	5	7 (1)	2	9
2	7 (1)	3	8 (1)	4
3	8	4	4	5
4	3	6	10	5
5	0	0	0	1
8-14	1	3	0	0
15-21	0	1	0	0
Median number of nights to positive mating sign	2.5	3	3	2
Number passing one oestrus	0	0	0	0
Number of males paired	24	24	24	24
Number of siring males	22	19	23	24
Male Fertility Index (%)	92	79	96	100
Number of females paired	24	24	24	24
Number pregnant	23	23	23	24
Female Fertility Index (%)	96	96	96	100

TABLE 25

610 P
Two Generation Reproduction Study in Rats
F_0 Generation, F_1 Production
Duration of Gestation and Overall Litter Performance

	Group/Dose Level (p.p.m. 610 P)			
	1 (0)	2 (1000)	3 (3000)	4 (10000)
Number Pregnant	28	26	27	27
Duration of Gestation (Days)				
21	11	10	15	10
22	14	14	12	17
23	3	1	0	0
24	0	1	0	0
Mean Duration	21.7	21.7	21.4	21.6
Number of females producing a live litter	28	26	27	27
Gestation index as %	100	100	100	100
Mean number of implant sites[a] per pregnancy ± standard deviation	15.9 ± 2.2	15.0 ± 2.1	15.8 ± 2.3	15.3 ± 2.2
Mean total number of pups born[a,b]	14.8 ± 2.1	13.4 ± 2.3	13.8 ± 3.4	14.0 ± 2.2
Mean number of live pups per litter ± standard deviation[a,b]:				
Day 0 of lactation	14.6 ± 2.1	13.0 ± 2.3	13.7 ± 3.3	13.5 ± 2.3
Day 1 of lactation	14.1 ± 2.1	12.9 ± 2.4	13.2 ± 3.3	13.3 ± 2.4
Day 4 of lactation	13.6 ± 1.8	12.3 ± 2.2	12.7 ± 3.4	12.7 ± 2.1
Day 7 of lactation	13.3 ± 1.9	12.2 ± 2.2	12.5 ± 3.6	12.5 ± 2.0
Day 14 of lactation	13.1 ± 1.9	12.0 ± 2.2	12.3 ± 3.6	12.1 ± 2.0
Day 21 of lactation	13.1 ± 1.9	12.0 ± 2.3	12.3 ± 3.7	12.0 ± 2.0

a = Excludes litters where all pups died
b = Excludes premature decedent (Animal 150)

TABLE 26

610 P
Two Generation Reproduction Study in Rats
F_1 Generation, F_2 Production
Duration of Gestation and Overall Litter Performance

	Group/Dose Level (p.p.m. 610 P)			
	1 (0)	2 (1000)	3 (3000)	4 (10000)
Number Pregnant	23	23	23	24
Duration of Gestation (Days)				
21	11	8	10	10
22	10	14	9	11
23	2	1	4	3
Mean Duration	21.6	21.7	21.7	21.7
Number of females producing a live litter	23	23	23	24
Gestation index as %	100	100	100	100
Mean number of implant sites[a] per pregnancy ± standard deviation	15.2 ± 2.2	15.7 ± 1.8	15.2 ± 3.2	14.8 ± 3.4
Mean total number of pups[a] born	14.3 ± 2.4	14.5 ± 1.9	13.6 ± 3.2	13.4 ± 3.6
Mean number of live pups[a] per litter ± standard deviation:				
Day 0 of lactation	14.3 ± 2.4	14.3 ± 1.9	13.5 ± 3.2	13.1 ± 3.8
Day 1 of lactation	14.0 ± 2.2	14.0 ± 2.1	13.0 ± 3.1	12.8 ± 3.7
Day 4 of lactation	13.2 ± 2.9	13.3 ± 2.5	12.7 ± 3.2	12.2 ± 4.0
Day 7 of lactation	13.1 ± 2.9	13.3 ± 2.5	12.5 ± 3.1	12.0 ± 4.1
Day 14 of lactation	13.4 ± 2.9	13.2 ± 2.5	12.3 ± 3.1	11.4 ± 3.9
Day 21 of lactation	13.0 ± 2.9	13.1 ± 2.6	12.3 ± 3.1	11.4 ± 3.9

a = Excludes litters where all pups died

TABLE 27

610 P
Two Generation Reproduction Study in Rats
F_1 Generation
Survival Indices

		Group/Dose Level (p.p.m. 610 P)			
		1 (0)	2 (1000)	3 (3000)	4 (10000)
Birth Index	Mean Litter Index (%)	94	90	90	92
	Number Losing >2 pups	3	4	5	3
	Number of Litters	27	24	26	26
Live Birth Index	Mean Litter Index (%)	97	96	100	96
	Number Losing >1 pup	2	3	1	3
	Number of Litters	28	26	27	27
Viability Index Days 0-4	Mean Litter Index (%)	91	90	90	95
	Number Losing >3 pups	3	2	2	0
	Number of Litters	28	26	27	27
Lactation Index Days 4-21	Mean Litter Index (%)	96	98	96	95
	Number Losing >1 pup	2	0	2	5
	Number of Litters	27	24	26	27
Overall Survival Index Birth-21	Mean Litter Index (%)	86	87	86	86
	Number Losing >4 pups	3	1	2	2
	Number of Litters	28	25	27	27

TABLE 28

610 P
Two Generation Reproduction Study in Rats
F_2 Generation
Survival Indices

		Group/Dose Level (p.p.m. 610 P)			
		1 (0)	2 (1000)	3 (3000)	4 (10000)
Birth Index	Mean Litter Index (%)	93	92	90	89
	Number Losing >2 pups	2	4	5	3
	Number of Litters	21	23	23	23
Live Birth Index	Mean Litter Index (%)	99	99	98	98
	Number Losing >1 pup	1	1	0	1
	Number of Litters	23	23	23	24
Viability Index Days 0-4	Mean Litter Index (%)	90	89	90	93
	Number Losing >3 pups	3	3	3	2
	Number of Litters	23	23	23	24
Lactation Index Days 4-21	Mean Litter Index (%)	98	98	97	93
	Number Losing >1 pup	1	1	1	6
	Number of Litters	22	22	22	24
Overall Survival Index Birth-21	Mean Litter Index (%)	88	86	87	86
	Number Losing >4 pups	3	1	3	2
	Number of Litters	23	23	23	24

TABLE 29

610 P
Two Generation Reproduction Study in Rats
F_1 Generation
Group Mean Litter and Pup Weight (g) ± Standard Deviation

Day of Lactation	Group/Dose Level (p.p.m. 610 P)			
	1 (0)	2 (1000)	3 (3000)	4 (10000)
LITTER				
Day 1	89 ± 12	83 ± 13	82 ± 19	86 ± 14
Day 4	124 ± 20	119 ± 26	114 ± 30	119 ± 16
Day 7	178 ± 30	173 ± 36	163 ± 44	167 ± 20
Day 14	345 ± 44	335 ± 56	320 ± 76	295 ± 32
Day 21	548 ± 76	543 ± 93	498 ± 121	451 ± 56
Mean of Litter Mean Pup Weight				
MALES				
Day 1	6.5 ± 0.6	6.7 ± 0.7	6.6 ± 0.8	6.8 ± 0.7
Day 4	9.4 ± 1.3	10.0 ± 1.4	9.3 ± 1.3	9.9 ± 1.3
Day 7	13.7 ± 1.8	14.6 ± 2.0	13.6 ± 2.0	14.0 ± 2.0
Day 14	27.0 ± 3.1	28.6 ± 3.3	27.1 ± 3.6	25.4 ± 3.1
Day 21	43.1 ± 6.1	46.9 ± 5.8	42.6 ± 7.2	39.3 ± 6.6
FEMALES				
Day 1	6.1 ± 0.6	6.3 ± 0.6	6.1 ± 0.6	6.3 ± 0.5
Day 4	8.9 ± 1.2	9.4 ± 1.3	8.8 ± 1.2	9.1 ± 1.2
Day 7	13.0 ± 1.7	13.8 ± 2.0	12.8 ± 1.9	13.2 ± 1.7
Day 14	26.0 ± 2.9	27.5 ± 3.3	26.0 ± 3.3	24.2 ± 3.1
Day 21	41.6 ± 5.7	44.7 ± 5.8	41.0 ± 6.3	37.4 ± 6.2

Means excludes litters where all pups died or were killed due to death of adult female

TABLE 30

610 P
Two Generation Reproduction Study in Rats
F_2 Generation
Group Mean Litter and Pup Weight (g) ± Standard Deviation

Day of Lactation	Group/Dose Level (p.p.m. 610 P)			
	1 (0)	2 (1000)	3 (3000)	4 (10000)
LITTER				
Day 1	73 ± 37	90 ± 13	82 ± 15	78 ± 21
Day 4	102 ± 56	127 ± 24	120 ± 23	108 ± 34
Day 7	152 ± 82	189 ± 30	179 ± 33	156 ± 50
Day 14	289 ± 154	358 ± 44	336 ± 51	274 ± 79
Day 21	456 ± 243	568 ± 63	535 ± 76	421 ± 120
Mean of Litter Mean Pup Weight				
MALES				
Day 1	6.6 ± 0.8	6.6 ± 0.6	6.6 ± 1.0	6.5 ± 1.1
Day 4	9.8 ± 1.4	9.9 ± 1.3	10.0 ± 2.0	9.5 ± 2.0
Day 7	14.8 ± 1.8	14.7 ± 1.9	15.1 ± 3.0	13.6 ± 2.9
Day 14	28.4 ± 3.0	28.1 ± 3.5	31.2 ± 13.0	25.4 ± 5.0
Day 21	45.0 ± 6.3	45.2 ± 6.5	46.1 ± 9.0	40.0 ± 9.2
FEMALES				
Day 1	6.3 ± 0.8	6.3 ± 0.7	6.3 ± 1.1	6.0 ± 0.8
Day 4	9.3 ± 1.5	9.4 ± 1.4	9.5 ± 2.1	8.7 ± 1.5
Day 7	13.9 ± 1.9	14.0 ± 2.0	14.5 ± 3.1	12.7 ± 2.2
Day 14	26.9 ± 3.2	27.2 ± 3.1	26.9 ± 6.4	23.9 ± 4.0
Day 21	42.9 ± 6.3	43.5 ± 6.2	44.3 ± 9.1	37.2 ± 7.8

Means exclude litters where all pups died

TABLE 31

610 P
Two Generation Reproduction Study in Rats
F_1 Generation
Assessment of Sexual Maturity

	Group/Dose Level (p.p.m. 610 P)			
	1 (0)	2 (1000)	3 (3000)	4 (10000)
Females				
Age at vaginal opening (days)	35.8 ± 3.2	35.1 ± 4.2	37.4 ± 3.2	37.8 ± 4.2
Weight (g) at vaginal opening	122 ± 19	117 ± 23	127 ± 15	128 ± 26
Males				
Age at preputial separation (days)	44.9 ± 1.7	45.0 ± 2.3	45.7 ± 1.9	46.3 ± 2.2
Weight (g) at preputial separation	220 ± 17	221 ± 18	223 ± 15	221 ± 18

All values given ± standard deviation

TABLE 32

610 P
Two Generation Reproduction Study in Rats
F_2 Generation
Assessment of Sexual Maturity

	Group/Dose Level (p.p.m. 610 P)			
	1 (0)	2 (1000)	3 (3000)	4 (10000)
Females				
Age at vaginal opening (days)	35.6 ± 2.8	35.6 ± 2.7	35.0 ± 2.4	36.2 ± 2.8
Weight (g) at vaginal opening	122 ± 16	119 ± 15	121 ± 17	120 ± 15
Males				
Age at preputial separation (days)	45.0 ± 2.6	45.5 ± 2.4	44.8 ± 2.1	46.0 ± 2.0
Weight (g) at preputial separation	222 ± 19	218 ± 19	222 ± 25	214 ± 22

All values given ± standard deviation

TABLE 33

610 P
Two Generation Reproduction Study in Rats
Fo Generation Males
Group Mean Absolute Organ Weights (g)

Group/ Dose Level (p.p.m. 610 P)		Body Weight (g)	Epididymides	Kidneys	Liver	Prostate	Seminal vesicle	Testes
1 (0)	Number	28	27	28	27	27	27	27
	Mean	583	1.5524	4.28	21.14	0.80	2.518	3.70
	SD	46	0.1477	0.37	3.17	0.24	0.528	0.29
2 (1000)	Number	28	28	28	28	27	27	28
	Mean	587	1.5883	4.34	21.96	0.82	2.527	3.77
	SD	68	0.2025	0.49	3.05	0.21	0.538	0.37
	Prob.							
3 (3000)	Number	28	28	28	28	28	28	28
	Mean	563	1.5229	4.24	21.97	0.85	2.378	3.64
	SD	39	0.1695	0.40	2.94	0.22	0.505	0.32
	Prob.							
4 (10000)	Number	28	28	28	28	28	28	28
	Mean	497	1.4502	4.00	19.77	0.69	2.053	3.62
	SD	58	0.1544	0.59	4.58	0.16	0.363	0.36
	Prob.	***	*	*			***	

Significantly different from the Control: * P<0.05, ** P<0.01, *** P<0.001

TABLE 34

610 P
Two Generation Reproduction Study in Rats
Fo Generation Males
Group Mean Adjusted Organ Weights

Group/ Dose Level (p.p.m. 610 P)		Body Weight (g)	Epididymides	Kidneys	Liver	Prostate	Seminal vesicle	Testes
1 (0)	Number	28	27	28	27	27	27	27
	Mean	558	1.5388	4.13	19.85	0.78	2.451	3.70
	SE	12	0.0331	0.07	0.43	0.04	0.093	0.07
2 (1000)	Number	28	28	28	28	27	27	28
	Mean	558	1.5711	4.17	20.46	0.80	2.448	3.76
	SE	12	0.0331	0.07	0.43	0.04	0.094	0.07
	Prob.							
3 (3000)	Number	28	28	28	28	28	28	28
	Mean	558	1.5194	4.21	21.69	0.84	2.362	3.64
	SE	12	0.0318	0.07	0.42	0.04	0.089	0.06
	Prob.				**			
4 (10000)	Number	28	28	28	28	28	28	28
	Mean	558	1.4841	4.36	22.80	0.73	2.210	3.62
	SE	12	0.0365	0.08	0.48	0.05	0.102	0.07
	Prob.				***			

Significantly different from the Control: * P<0.05, ** P<0.01, *** P<0.001

TABLE 35

610 P
Two Generation Reproduction Study in Rats
F1 Generation Males
Group Mean Absolute Organ Weights (g)

Group/ Dose Level (p.p.m. 610 P)		Body Weight (g)	Epididymides	Kidneys	Liver	Prostate Gland	Seminal Vesicles	Testes
1 (0)	Number	24	24	24	24	24	24	24
	Mean	564	1.4668	3.98	22.00	0.88	2.601	3.65
	SD	56	0.1535	0.51	2.76	0.21	0.491	0.37
2 (1000)	Number	24	24	24	24	24	24	24
	Mean	552	1.4760	4.01	20.88	0.89	2.682	3.68
	SD	51	0.1102	0.49	2.55	0.21	0.487	0.24
	Prob.							
3 (3000)	Number	24	24	24	24	24	24	24
	Mean	561	1.5138	4.20	21.74	0.83	2.458	3.71
	SD	58	0.1450	0.47	2.85	0.20	0.611	0.29
	Prob.							
4 (10000)	Number	24	24	24	24	24	24	24
	Mean	486	1.4431	3.93	18.61	0.68	2.109	3.83
	SD	48	0.1406	0.65	3.08	0.17	0.538	0.30
	Prob.	***			***	***	**	

Significantly different from the Control: * P<0.05, ** P<0.01, *** P<0.001

TABLE 36

610 P
Two Generation Reproduction Study in Rats
F1 Generation Males
Group Mean Adjusted Organ Weights

Group/ Dose Level (p.p.m. 610 P)		Body Weight (g)	Epididymides	Kidneys	Liver	Prostate Gland	Seminal Vesicles	Testes
1 (0)	Number	24	24	24	24	24	24	24
	Mean	541	1.4486	3.82	21.11	0.88	2.583	3.61
	SE	13	0.0277	0.08	0.41	0.04	0.112	0.06
2 (1000)	Number	24	24	24	24	24	24	24
	Mean	541	1.4672	3.93	20.45	0.89	2.673	3.66
	SE	13	0.0272	0.08	0.40	0.04	0.110	0.06
	Prob.							
3 (3000)	Number	24	24	24	24	24	24	24
	Mean	541	1.4980	4.06	20.97	0.83	2.442	3.68
	SE	13	0.0275	0.08	0.40	0.04	0.111	0.06
	Prob.			*				
4 (10000)	Number	24	24	24	24	24	24	24
	Mean	541	1.4859	4.30	20.71	0.69	2.151	3.91
	SE	13	0.0305	0.09	0.45	0.05	0.123	0.07
	Prob.			***		**	*	**

Significantly different from the Control: * P<0.05, ** P<0.01, *** P<0.001

TABLE 37

610 P
Two Generation Reproduction Study in Rats
F2 Generation Males
Group Mean Absolute Organ Weights (g)

Group/ Dose Level (p.p.m. 610 P)		Body Weight (g)	Epididymides	Kidneys	Liver	Prostate Gland	Seminal Vesicles	Testes
1 (0)	Number	22	22	22	22	22	22	22
	Mean	253	0.3658	2.61	14.91	0.24	0.576	2.38
	SD	24	0.0523	0.29	2.08	0.06	0.144	0.22
2 (1000)	Number	22	22	22	22	22	22	22
	Mean	244	0.3391	2.46	14.14	0.21	0.497	2.32
	SD	19	0.0487	0.19	1.66	0.04	0.130	0.27
	Prob.							
3 (3000)	Number	22	22	22	22	22	22	22
	Mean	252	0.3743	2.61	15.81	0.22	0.483	2.34
	SD	34	0.0642	0.31	3.07	0.06	0.164	0.28
	Prob.						*	
4 (10000)	Number	24	24	24	24	24	24	24
	Mean	235	0.3383	2.36	15.33	0.20	0.437	2.22
	SD	22	0.0577	0.24	2.02	0.05	0.114	0.28
	Prob.			**			**	

Significantly different from the Control: * P<0.05, ** P<0.01, *** P<0.001

TABLE 38

610 P
Two Generation Reproduction Study in Rats
F2 Generation Males
Group Mean Adjusted Organ Weights

Group/ Dose Level (p.p.m. 610 P)		Body Weight (g)	Epididymides	Kidneys	Liver	Prostate Gland	Seminal Vesicles	Testes
1 (0)	Number	22	22	22	22	22	22	22
	Mean	246	0.3552	2.54	14.44	0.23	0.551	2.34
	SE	6	0.0092	0.03	0.34	0.01	0.024	0.05
2 (1000)	Number	22	22	22	22	22	22	22
	Mean	246	0.3418	2.48	14.25	0.21	0.503	2.33
	SE	6	0.0091	0.03	0.34	0.01	0.024	0.05
	Prob.							
3 (3000)	Number	22	22	22	22	22	22	22
	Mean	246	0.3654	2.56	15.41	0.22	0.462	2.31
	SE	6	0.0092	0.03	0.34	0.01	0.024	0.05
	Prob.				*		**	
4 (10000)	Number	24	24	24	24	24	24	24
	Mean	246	0.3538	2.45	16.02	0.21	0.472	2.27
	SE	5	0.0090	0.03	0.33	0.01	0.023	0.05
	Prob.				**		*	

Significantly different from the Control: * P<0.05, ** P<0.01, *** P<0.001

TABLE 39

610 P
Two Generation Reproduction Study in Rats
Fo Generation Females
Group Mean Absolute Organ Weights (g)

Group/ Dose Level (p.p.m. 610 P)		Body Weight (g)	Kidneys	Liver
1 (0)	Number	27	27	27
	Mean	310	2.59	16.11
	SD	27	0.24	2.17
2 (1000)	Number	24	24	24
	Mean	329	2.75	17.45
	SD	30	0.25	2.15
	Prob.	*	*	*
3 (3000)	Number	26	26	26
	Mean	325	2.87	18.75
	SD	26	0.21	2.84
	Prob.	*	***	***
4 (10000)	Number	27	27	27
	Mean	317	2.90	22.47
	SD	21	0.34	2.29
	Prob.		***	***

Significantly different from the Control: * P<0.05, ** P<0.01, *** P<0.001

TABLE 40

610 P
Two Generation Reproduction Study in Rats
Fo Generation Females
Group Mean Adjusted Organ Weights

Group/ Dose Level (p.p.m. 610 P)		Body Weight (g)	Kidneys	Liver
1 (0)	Number	27	27	27
	Mean	320	2.65	16.67
	SE	5	0.04	0.37
2 (1000)	Number	24	24	24
	Mean	320	2.70	16.95
	SE	5	0.05	0.39
	Prob.			
3 (3000)	Number	26	26	26
	Mean	320	2.84	18.44
	SE	5	0.04	0.38
	Prob.		**	**
4 (10000)	Number	27	27	27
	Mean	320	2.92	22.64
	SE	5	0.04	0.37
	Prob.		***	***

Significantly different from the Control: * P<0.05, ** P<0.01, *** P<0.001

TABLE 41

610 P
Two Generation Reproduction Study in Rats
F1 Generation Females
Group Mean Absolute Organ Weights (g)

Group/ Dose Level (p.p.m. 610 P)		Body Weight (g)	Kidneys	Liver
1 (0)	Number	22	22	22
	Mean	307	2.45	15.12
	SD	32	0.27	2.13
2 (1000)	Number	22	22	22
	Mean	311	2.61	16.77
	SD	28	0.27	2.68
	Prob.			*
3 (3000)	Number	22	22	22
	Mean	308	2.62	17.23
	SD	23	0.26	2.69
	Prob.			**
4 (10000)	Number	24	24	24
	Mean	291	2.54	20.01
	SD	24	0.20	2.44
	Prob.			***

Significantly different from the Control: * P<0.05, ** P<0.01, *** P<0.001

TABLE 42

610 P
Two Generation Reproduction Study in Rats
F1 Generation Females
Group Mean Adjusted Organ Weights

Group/ Dose Level (p.p.m. 610 P)		Body Weight (g)	Kidneys	Liver
1 (0)	Number	22	22	22
	Mean	304	2.44	15.00
	SE	6	0.04	0.48
2 (1000)	Number	22	22	22
	Mean	304	2.57	16.49
	SE	6	0.04	0.49
	Prob.		*	*
3 (3000)	Number	22	22	22
	Mean	304	2.59	17.07
	SE	6	0.04	0.48
	Prob.		**	**
4 (10000)	Number	24	24	24
	Mean	304	2.62	20.52
	SE	6	0.04	0.48
	Prob.		**	***

Significantly different from the Control: * P<0.05, ** P<0.01, *** P<0.001

TABLE 43

610 P
Two Generation Reproduction Study in Rats
F2 Generation Females
Group Mean Absolute Organ Weights (g)

Group/ Dose Level (p.p.m. 610 P)		Body Weight (g)	Kidneys	Liver
1 (0)	Number	22	22	22
	Mean	168	1.78	9.78
	SD	16	0.21	1.12
2 (1000)	Number	22	22	22
	Mean	163	1.75	9.46
	SD	15	0.16	1.39
	Prob.			
3 (3000)	Number	22	22	21
	Mean	172	1.89	10.49
	SD	16	0.23	1.46
	Prob.			
4 (10000)	Number	23	23	23
	Mean	168	1.82	10.80
	SD	17	0.25	1.42
	Prob.			*

Significantly different from the Control: * P<0.05, ** P<0.01, *** P<0.001

TABLE 44

610 P
Two Generation Reproduction Study in Rats
F2 Generation Females
Group Mean Adjusted Organ Weights

Group/ Dose Level (p.p.m. 610 P)		Body Weight (g)	Kidneys	Liver
1 (0)	Number	22	22	22
	Mean	168	1.78	9.77
	SE	3	0.03	0.18
2 (1000)	Number	22	22	22
	Mean	168	1.80	9.77
	SE	3	0.03	0.18
	Prob.			
3 (3000)	Number	22	22	21
	Mean	168	1.84	10.18
	SE	3	0.03	0.19
	Prob.			
4 (10000)	Number	23	23	23
	Mean	168	1.82	10.80
	SE	3	0.03	0.18
	Prob.			***

Significantly different from the Control: * P<0.05, ** P<0.01, *** P<0.001

TABLE 45

610 P
Two Generation Reproduction Study in Rats
F1 Generation Unselected Males
Group Mean Testes Weights (g)

Group/ Dose Level (p.p.m. 610 P)		Body Weight (g)	Testes
1 (0)	Number	27	27
	Mean	68	0.42
	SD	8	0.07
2 (1000)	Number	23	23
	Mean	70	0.41
	SD	9	0.07
	Prob.		
3 (3000)	Number	26	26
	Mean	69	0.42
	SD	10	0.11
	Prob.		
4 (10000)	Number	27	27
	Mean	65	0.35
	SD	11	0.10
	Prob.		**

Significantly different from the Control: * P<0.05, ** P<0.01, *** P<0.001

TABLE 46

610 P
Two Generation Reproduction Study in Rats
F1 Generation Unselected Males
Group Mean Adjusted Testes Weights

Group/ Dose Level (p.p.m. 610 P)		Body Weight (g)	Testes
1 (0)	Number	27	27
	Mean	68	0.42
	SE	2	0.01
2 (1000)	Number	23	23
	Mean	68	0.40
	SE	2	0.01
	Prob.		
3 (3000)	Number	26	26
	Mean	68	0.41
	SE	2	0.01
	Prob.		
4 (10000)	Number	27	27
	Mean	68	0.38
	SE	2	0.01
	Prob.		**

Significantly different from the Control: * P<0.05, ** P<0.01, *** P<0.001

TABLE 47

610 P
Two Generation Reproduction Study in Rats
F2 Generation Unselected Males
Group Mean Testes Weights (g)

Group/ Dose Level (p.p.m. 610 P)		Body Weight (g)	Testes
1 (0)	Number	21	21
	Mean	76	0.48
	SD	12	0.11
2 (1000)	Number	22	22
	Mean	77	0.47
	SD	12	0.11
	Prob.		
3 (3000)	Number	22	22
	Mean	75	0.46
	SD	14	0.13
	Prob.		
4 (10000)	Number	23	23
	Mean	71	0.40
	SD	10	0.10
	Prob.		

TABLE 48

610 P
Two Generation Reproduction Study in Rats
F2 Generation Unselected Males
Group Mean Adjusted Testes Weights

Group/ Dose Level (p.p.m. 610 P)		Body Weight (g)	Testes
1 (0)	Number	21	21
	Mean	75	0.47
	SE	3	0.01
2 (1000)	Number	22	22
	Mean	75	0.45
	SE	3	0.01
	Prob.		
3 (3000)	Number	22	22
	Mean	75	0.45
	SE	3	0.01
	Prob.		
4 (10000)	Number	23	23
	Mean	75	0.43
	SE	3	0.01
	Prob.		

TABLE 49

610 P
Two Generation Reproduction Study in Rats
F0 Generation: Group Incidence of Necropsy Findings

FINDINGS	TREATMENT	INCIDENCE OF MACROSCOPIC FINDINGS (NUMERIC)							
		MALES				FEMALES			
		Grp 1 0 p.p.m.	Grp 2 1000 p.p.m.	Grp 3 3000 p.p.m.	Grp 4 10000 p.p.m.	Grp 1 0 p.p.m.	Grp 2 1000 p.p.m.	Grp 3 3000 p.p.m.	Grp 4 10000 p.p.m.
ALL ORGANS:									
No abnormality detected		27	20	24	5	25	28	25	27
KIDNEY:									
Both dark					1				
Both have pelvic dilation			1		1				
Right has cyst			1			1			
LIVER:									
Discoloured					2				
Pale					15				
Enlarged					2				
Prominent lobulation					10				
Pale focus(i) at bifurcation of median lobe								2	1
Pale focus(i)					2			1	
Dark focus(i)					8				
OTHER SITES:									
TEETH: Enlarged					1				

The absence of a numeral indicates that the finding specified was not identified.

TABLE 49 (continued)

F0 Generation: Group Incidence of Necropsy Findings

FINDINGS	TREATMENT	INCIDENCE OF MACROSCOPIC FINDINGS (NUMERIC)							
		MALES				FEMALES			
		Grp 1 0 p.p.m.	Grp 2 1000 p.p.m.	Grp 3 3000 p.p.m.	Grp 4 10000 p.p.m.	Grp 1 0 p.p.m.	Grp 2 1000 p.p.m.	Grp 3 3000 p.p.m.	Grp 4 10000 p.p.m.
PROSTATE:									
Reddened			1						
Small		1							
SEMINAL VESICLE:									
Reddened			1						
Small			1						
SKIN AND SUBCUTIS:									
Staining			7	3	1				
TESTIS:									
Right discoloured					1				
One/both flaccid					2				
Left small				1					
UTERUS:									
Both horns dilated						2			

The absence of a numeral indicates that the finding specified was not identified.

TABLE 50

610 P
Two Generation Reproduction Study in Rats
F0 Generation: Group Incidence of Histology Findings

FINDINGS	TREATMENT	INCIDENCE OF LESIONS (NUMERIC)							
		MALES				FEMALES			
		Grp 1 0 p.p.m.	Grp 2 1000 p.p.m.	Grp 3 3000 p.p.m.	Grp 4 10000 p.p.m.	Grp 1 0 p.p.m.	Grp 2 1000 p.p.m.	Grp 3 3000 p.p.m.	Grp 4 10000 p.p.m.
CERVIX:						(28)			(28)
No abnormality detected						28			28
COAGULATING GLANDS:		(27)			(28)				
No abnormality detected		27			28				
EPIDIDYMIS:		(28)			(28)				
No abnormality detected		28			26				
Reduced sperm		0			2				
KIDNEY:					(2)	(1)			
Pelvic dilation					1	0			
Basophilic tubules					1	0			
Focal nephropathy					0	1			
Focal inflammatory cell infiltration					1	0			
Cyst					0	1			
(Macroscopic finding not confirmed histologically)					1	0			

Figures in brackets represent the number of animals from which this tissue was examined histologically.
Significance of differences in a pairwise (Fisher's) test between control and each treatment group: * P<0.05, ** P<0.01, *** P<0.001

TABLE 51

610 P
Two Generation Reproduction Study in Rats
F1 Generation: Group Incidence of Necropsy Findings

FINDINGS	TREATMENT	INCIDENCE OF MACROSCOPIC FINDINGS (NUMERIC)							
		MALES				FEMALES			
		Grp 1 0 p.p.m.	Grp 2 1000 p.p.m.	Grp 3 3000 p.p.m.	Grp 4 10000 p.p.m.	Grp 1 0 p.p.m.	Grp 2 1000 p.p.m.	Grp 3 3000 p.p.m.	Grp 4 10000 p.p.m.
ALL ORGANS:									
No abnormality detected		22	21	19	6	21	20	19	17
INTESTINES:									
Distended						1			
KIDNEY:									
Both speckled				1					
One/both have pelvic dilation					2				
LIVER:									
Pale				1	15				
Pale focus(i) at bifurcation of median lobe			1	2	2		2	1	4
Pale focus(i)					1			1	
Dark focus(i)					1				
LUNG:									
Pale focus(i)								1	1

The absence of a numeral indicates that the finding specified was not identified.

TABLE 51 (continued)

F1 Generation: Group Incidence of Necropsy Findings

FINDINGS	TREATMENT	INCIDENCE OF MACROSCOPIC FINDINGS (NUMERIC)							
		MALES				FEMALES			
		Grp 1 0 p.p.m.	Grp 2 1000 p.p.m.	Grp 3 3000 p.p.m.	Grp 4 10000 p.p.m.	Grp 1 0 p.p.m.	Grp 2 1000 p.p.m.	Grp 3 3000 p.p.m.	Grp 4 10000 p.p.m.
LYMPH NODE(S):									
HEPATIC: enlarged					1				
OTHER SITES:									
EAR(S): right Lesion		1							
EAR(S): both reddened							1		
MOUTH: Teeth Mis-aligned						1			
SKIN AND SUBCUTIS:									
Scab(s)			1						
Hair loss					1	1	1	1	1
Bald area		1							
Staining				1					3
SUBMANDIBULAR LYMPH NODE:									
Enlarged								1	
UTERUS:									
Distended							1		

The absence of a numeral indicates that the finding specified was not identified.

TABLE 52 (continued)

F1 Generation: Group Incidence of Histology Findings

FINDINGS	TREATMENT	INCIDENCE OF LESIONS (NUMERIC)							
		MALES				FEMALES			
		Grp 1 0 p.p.m.	Grp 2 1000 p.p.m.	Grp 3 3000 p.p.m.	Grp 4 10000 p.p.m.	Grp 1 0 p.p.m.	Grp 2 1000 p.p.m.	Grp 3 3000 p.p.m.	Grp 4 10000 p.p.m.
TESTIS:		(24)			(23)				
Total incidence for score expanded finding		4			4				
Focal bilateral tubular atrophy		2			0				
Diffuse unilateral tubular atrophy moderate		1			0				
Total incidence for score expanded finding		1			0				
UTERUS:						(24)			(22)
No abnormality detected						22			15
Dilation in one/both horns						1			4
Dilated/cystic gland(s)						1			2
Haemosiderin						1			2
VAGINA:						(24)			(22)
No abnormality detected						24			22
Metoestrus						6			4
Oestrus						4			4
Dioestrus						8			5
Proestrus						6			9

Figures in brackets represent the number of animals from which this tissue was examined histologically.
Significance of differences in a pairwise (Fisher's) test between control and each treatment group: * P<0.05, ** P<0.01, *** P<0.001

TABLE 53

610 P
Two Generation Reproduction Study in Rats
F2 Generation: Group Incidence of Necropsy Findings

FINDINGS	TREATMENT	INCIDENCE OF MACROSCOPIC FINDINGS (NUMERIC)							
		MALES				FEMALES			
		Grp 1 0 p.p.m.	Grp 2 1000 p.p.m.	Grp 3 3000 p.p.m.	Grp 4 10000 p.p.m.	Grp 1 0 p.p.m.	Grp 2 1000 p.p.m.	Grp 3 3000 p.p.m.	Grp 4 10000 p.p.m.
ALL ORGANS:									
No abnormality detected		20	16	14	10	20	19	19	22
KIDNEY:									
Both dilated			1						
Right pale			1						
One/both flaccid		1	1	2					1
Left enlarged				1					
One/both have pelvic dilation			2	1	4	1	3	1	
Right has cyst		1							
LIVER:									
Pale				2	1				
Prominent lobulation				3	10				
Pale focus(i) at bifurcation of median lobe				1	1				
LUNG:									
Pale				1					

The absence of a numeral indicates that the finding specified was not identified.

TABLE 53 (continued)

F2 Generation: Group Incidence of Necropsy Findings

FINDINGS	TREATMENT	INCIDENCE OF MACROSCOPIC FINDINGS (NUMERIC)							
		MALES				FEMALES			
		Grp 1 0 p.p.m.	Grp 2 1000 p.p.m.	Grp 3 3000 p.p.m.	Grp 4 10000 p.p.m.	Grp 1 0 p.p.m.	Grp 2 1000 p.p.m.	Grp 3 3000 p.p.m.	Grp 4 10000 p.p.m.
OTHER SITES:									
TAIL: discoloured					1				
TESTIS:									
Left small			1						
UTERUS:									
Distended						1	1	2	

The absence of a numeral indicates that the finding specified was not identified.