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TOXICOLOGY DEPARTMENT
P.O. BOX 12014, 2 T.W. ALEXANDER DRIVE
RESEARCH TRIANGLE PARK, NC 27709
(919) 549-2000 TELEFAX (919) 549-8525
INTERNATIONAL TELEX NUMBER 4999378-ANSWERBACK APC RTP

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US Environmental Protection Agency
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Attn: Section 8(e) Coordinator (CAP Agreement)

RE: Report Submitted Pursuant to the TSCA Section 8(e) Compliance Audit Program

CAP ID No.: 8ECAP - 0004

Dear Sir/Madam:

On behalf of Rhône-Poulenc Inc. (RPI, CN 5266, Princeton, NJ 08543-5266) and its subsidiary Rhône-Poulenc Ag Company (RPAC), the attached study report is being submitted to the Environmental Protection Agency (EPA) pursuant to the Toxic Substances Control Act (TSCA) Section 8(e) Compliance Audit Program and the Agreement for a TSCA Section 8(e) Compliance Audit Program (CAP Agreement) executed by RPI and EPA.

The enclosed study report provides information on ioxynil. The CAS number assigned to this compound is 1689-83-4. The CAS name is 4-hydroxy-3,5-diiodobenzonitrile. This chemical was manufactured in Europe and imported by RPAC for pesticide research and development. We have never filed a pesticide application to EPA under the Federal Insecticide, Fungicide, and Rodenticide Act.

No claims of confidentiality are made for this submission. The title of the enclosed report is "Ioxynil Technical: Teratogenicity Study with Littering Phase, by the Oral Route, in the Rat". The following is a summary of the adverse effects observed in this study.

This study is being submitted under Section 8(e) because of a statistically significant treatment-related reduction in fetal weights and statistically significant increases in hydroureter and supernumerary ribs at the only dose tested (35 mg/kg/day).

Rats were dosed once per day by gavage on gestation days 5 through 17 with either 35 mg/kg/day or vehicle only (49 females/group). A portion of the animals in each group were killed on gestation day 22 and had their litters removed by caesarean section. The remaining animals were allowed to deliver and rear their young to weaning. All surviving dams and pups were sacrificed on day 21 post-partum. Skeletal evaluations were performed on all pups.

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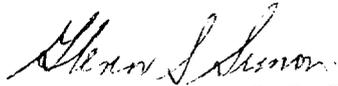
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Maternal toxicity observed at 35 mg/kg/day consisted of reductions in body weight gain during the gestation period and a transient reduction in food intake during the first few days of dosing. For animals sacrificed on gestation day 22, fetal weight was significantly lower in the ioxynil group compared to control. Minor anomalies were slightly, but not statistically, increased in the treated group. The incidence of hydroureter was statistically increased when compared to control. The incidence of supernumerary ribs was significantly increased for both fetuses and pups from the treated group. No other treatment-related effects were noted in the study.

No previous TSCA Section 8(e) notices have been submitted on this chemical, but seven submissions will be made on ioxynil under the CAP. In total, RPI is submitting three copies of the enclosed report and this cover letter: an original and two copies.

Further questions regarding this submission may be directed to the undersigned at 919-549-2222.

Sincerely,



Glenn S. Simon, PhD, DABT
Director of Toxicology



M&B May & Baker

Report Ref. R.Tox.89
 Copy No. 17
 Pages 1-82

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Ioxynil technical:

Teratogenicity study with littering phase, by the
 oral route, in the rat.

Scientific report from the Research Laboratories
 of
 May & Baker Ltd.

by
 G.P. Copping, H.N.D.

Histopathological examinations were carried out by

Dr. M.P. James, B.V.Sc., Ph.D., M.R.C.V.S.,
 Comparative Pathology Laboratory,
 University of Bristol

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The present format of this report is unsuitable for presentation to a Registration Authority.

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SUMMARY

In a comparative study, the induction, by ioxynil technical, of hydroureter and supernumerary ribs in the rat, as reported before (Copping, 1981), was reassessed in terms of post-parturition development.

Animals were dosed once on each of days 5 to 17 post-coitum with 35 mg/kg ioxynil technical or vehicle only. A proportion of animals in each group were killed on day 22 post-coitum and had their litters removed by caesarean section. The remaining animals were allowed to deliver and rear their young to weaning. Post-parturition developmental tests were conducted on all pups.

Maternal observations from both phases (teratology and littering) at 35 mg/kg ioxynil technical paralleled those seen before, i.e. reduction in bodyweight gain throughout the dosing and post-dosing periods, and reduced food intake during the initial part of the dosing period.

Litter parameters (teratology phase) remained essentially unaffected by treatment, although a repetition of the previously observed reduction in mean foetal weight was recorded.

Post-parturition data were essentially comparable between the control and treated groups, mean pup and litter weights being very similar.

The incidence of hydroureter observed in day 22 post-coitum pups showed a statistically significant increase of the same order as seen before, at 35 mg/kg ioxynil technical, although no cases were observed in any littering phase animals, pup maturity as indicated by bodyweight at birth being similar for each group.

The types and numbers of supernumerary 14th rib variants were very similar to those seen before at 35 mg/kg ioxynil technical in both study phases.

The incidence of hydroureter in day 22 post-coitum fetuses, possibly due to delayed rupture of ureteric membranes or some transitory biochemical deficiency, may possibly be linked with the reduced foetal weight observed. Both possibilities are well documented (Monie et al, 1957, Giroud, A., 1960 and Warkany, J., 1971).

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INTRODUCTION

A previous study (Copping, 1981) assessed the effects of daily oral dosages, administered on days 5-17 post-coitum inclusive, of 0, 5, 15 or 35 mg/kg ioxynil technical on pregnancy of the rat. The results showed a degree of maternal toxicity at the highest dosage, and an effect upon the foetus as exhibited by an increased incidence of hydroureter, and other associated minor anomalies. A dose related trend in the incidence of the supernumerary 14th rib variant was also associated with treatment at all dosages of ioxynil technical tested.

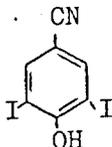
This report describes a study designed to discover whether such anomalies (hydroureter, supernumerary 14th ribs) affect post-parturition development of the offspring.

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1. MATERIALS

Ioxynil is 3,5-diiodo-4-hydroxybenzonitrile.



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Material from batch number LN 1024 was used in this study.

Analytical data for the batch used are given in Analytical Report CJB/WG of the 7th January 1981 (see Appendix I).

Throughout the report, for reasons of consistency and convenience, all dosages are expressed in terms of ioxynil technical (i.e. the actual test substance).

The ioxynil technical used in the study was associated with 10.6% water and volatiles (loss on drying at 105°C) and a further 1.5% w/v of related impurities were assayed with reference to the dried material (Appendix I).

Thus, the dosage of 35 mg/kg ioxynil technical corresponds to 30.8 mg/kg ioxynil pure (e.g. $35 \times \frac{89.4}{100} \times \frac{98.5}{100} = 30.82$)

2. METHODS

(Protocol Ref : STUDY/TA/81/003/01 with amendments /02 and /03)

All methodology was according to Standard Operating Procedures.

2.1 Animals

Ninety eight mated female CD strain rats (Sprague Dawley origin), received on the 13th and 27th February 1981, and each weighing approximately 200 g, were obtained from Charles River (U.K.) Ltd., Margate, Kent, on days 1, 2, 3 or 4 post-coitum (day 1 being the day on which evidence of mating was found).

Details of the sires were not known.

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2.2 Animal accommodation

The rats were housed in fours (teratology phase) or individually (littering phase) in metal cages with grid floors, suspended over trays containing sawdust. On day 15 post-coitum, littering females were transferred to cages with solid metal floors and provided with Grade 6 sawdust from Sawdust Marketing Company Ltd., Standon, Herts. (see Appendix II) and Kleenex Medical Wipes, Kimberly Clark Ltd., Larkfield, Maidstone, Kent. Samples of raw timber had been analysed for dieldrin and pentachlorophenol content.

The cleaning of littering phase cages ceased once littering commenced so as to avoid unnecessary disturbance of dam and litter, and was resumed on day 4 post-partum

All animals were housed in room K5 of D47 Building of the Research Institute, May & Baker Ltd., Dagenham. The room had forced air ventilation, and a daily photoperiod of 14 hours (06.00 to 20.00 h) was maintained by time switch controlled, fluorescent lighting. Daily temperature was in the region of 18°C; humidity was not controlled. Both parameters were continuously recorded.

2.3 Diet and water

Expanded pelleted rodent diet CRMX, from Labsure Diets, a member of the Christopher Hill Group (RHM), Poole, Dorset, and tap water were available to the rats at all times.

Diet and water samples were analysed for heavy metals, pesticide and other contaminants quoted in the Federal Register (July 1979), and certificates of analysis were obtained (Appendices III and IV).

Concentrations of some dietary ingredients were compared with the limits quoted in the Laboratory Animals Centre Diets Advisory Committee Report (1977).

2.4 Dosing

The rats were individually identified by an ear clipping system and randomly assigned to two treatment groups, each of 49 animals. Dosing occurred between 14th February and 15th March 1981.

Rats were dosed orally once on each of days 5-17 post-coitum, by means of a metal oesophageal tube, with either the vehicle or 35 mg ioxynil technical per kilogram bodyweight in the form of an aqueous suspension containing 0.25% w/v gum tragacanth. Suspensions were prepared freshly each week and refrigerated each day after use. Throughout the report dosages are expressed as mg ioxynil technical per kg bodyweight.

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Control rats received the vehicle only.

The volume administered to each rat was 5 ml per kilogram bodyweight per day (0 or 0.7% w/v ioxynil technical).

Dosages were adjusted according to the animals bodyweight on the day of dosing.

Prior to the start of dosing, and at weekly intervals throughout the dosing period, samples of the test material suspension were collected for later analysis and confirmation of ioxynil technical content (Appendix V).

2.5 Observations

2.5.1 Bodyweight and food consumption

Bodyweight and food consumption data for all rats were recorded to the nearest gram upon receipt and on days 5, 8, 11, 14, 18 and 22 post-coitum. Post-parturition bodyweights of dams and individual pups were recorded on days 0 or 1, 4, 8, 12, 16 and 21 post-partum.

No post-parturition food consumption data were recorded.

2.5.2 General observations

All animals were observed daily, and any animals dying or found dead were subjected to a gross necropsy unless this was prevented by cannibalism or autolytic degeneration.

Littering phase animals were observed regularly from day 22 post-coitum for onset of parturition.

After parturition dams and litters were checked regularly for assessment of health. Any dead or missing pups were recorded. Dead pups were weighed, sexed and examined externally and by dissection, if possible, so as to ascertain the cause of death.

All dead pups, where possible, were stained with alizarin red S (Dawson 1926) for subsequent skeletal examination.

2.5.3 Teratology phase

The teratology phase rats were killed on day 22 post-coitum (3rd March to 5th March 1981) by carbon dioxide asphyxiation, and subjected to a gross necropsy. Their uteri and ovaries were removed.

The numbers of corpora lutea, viable foetuses and early and late uterine deaths were recorded. Early uterine deaths were defined as those implantations without, and late deaths those with, embryonal or foetal elements.

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Individual viable foetuses were weighed, sexed and examined in detail for external abnormalities and by dissection, after an intrathoracic injection of sodium pentobarbitone solution ('Euthatal' ex May & Baker Ltd.).

Any abnormalities of placentation or amniotic structure were noted. The brains of all viable foetuses were examined by free hand sectioning after fixation in Bouin's fluid, and the skeletons by examination under a dissecting microscope after staining with alizarin red S (Dawson 1926).

2.5.4 Littering phase

The littering phase rats were checked approximately hourly on days 22 and 23 post-coitum for onset of parturition. Where possible parturition was observed (this being defined as day 0 post-partum) and the approximate duration calculated.

As soon as possible after parturition was complete the offspring were counted, sexed, weighed and examined for external abnormalities. Any dead or stillborn pups were noted, dead animals being sexed and weighed if possible. Daily records were kept of mortality and litter size.

If parturition was not complete by 16.00 h on any given day, examinations took place on day 1 post-partum.

2.5.5 Pre-weaning development and behavioural tests

The rate of physical development and sensory function of the offspring was assessed in terms of pinna unfolding, hair growth, tooth eruption, eye opening, surface righting and air righting reflexes and startle response.

2.5.6 Littering phase necropsies

On day 21 post-partum, or thereabouts, dams and litters were killed by carbon dioxide asphyxiation and subjected to a gross necropsy. In addition, all pups were examined after staining with alizarin red S (Dawson 1926) for assessment of supernumerary 14th ribs.

2.5.7 Histopathology

Following fixation, tissue selected for microscopic examination from either study phase, was routinely processed, sectioned and appropriately stained.

Histopathological evaluation of the prepared tissue was made by Dr. M.P. James, Comparative Pathology Laboratory, University of Bristol.

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3. CALCULATIONS

3.1 Teratology phase

3.1.1 For each litter pre-implantation loss was defined as:

$$\frac{\text{No. of corpora lutea} - \text{No. of implantations}}{\text{No. of corpora lutea}} \times 100$$

When the number of implantations exceeds the number of corpora lutea, pre-implantation loss is taken as zero.

3.1.2 For each litter post-implantation loss was defined as:

$$\frac{\text{No. of implantations} - \text{No. of viable foetuses}}{\text{No. of implantations}} \times 100$$

3.1.3 Calculations of mean data were as follows:

i) Method A was applied to obtain a mean value of foetal weight for each litter.

$$\frac{\text{Total weight of viable foetuses in litter}}{\text{Total number of viable foetuses in litter}}$$

ii) Method B was applied to obtain an overall group mean foetal weight, pre-implantation (%) or post-implantation (%) loss.

$$\frac{\text{Sum of litter mean or percentage for group } x}{\text{Total number of litters in group } x}$$

iii) Method C was applied to obtain a group mean percentage for major malformation or minor anomaly for each group.

$$\frac{\text{Sum of \% incidence of major malformation or minor anomaly for litters in group } x}{\text{Total number of litters examined in group } x}$$

3.2 Littering phase

Females permitted to deliver their offspring normally provided information on gestation length, parturition, litter size at birth, birth

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weight, viability, incidence of abnormal young and post-parturition development. The methods of calculation given below differ from the methods outlined in the protocol in that calculations are on a group basis only, and not as a mean of litter means.

- i) Viability index (calculated for each group from individual data):

$$\frac{\text{Total no. viable offspring in group on day of examination}}{\text{Total no. viable offspring at 24 h post-partum}} \times 100$$

- ii) Live birth index:

$$\frac{\text{Total no. viable offspring in group at 24 h post-partum}}{\text{Total no. offspring born (group)}} \times 100$$

- iii) Lactation index:

Percentage of offspring that were alive at 4 days, that survived the 21 day lactation period.

$$\frac{\text{Total no. animals in group on day 21 post-partum}}{\text{Total no. animals in group on day 4 post-partum}} \times 100$$

3.3 Food consumption calculations

Food consumption was calculated on a gram/cage/day basis for pregnant and non-pregnant animals (teratology phase), this being divided by the number of 'rat-days' to give a gram/rat/day figure. Food consumption calculations (littering phase) were performed for pregnant animals only. Any animal dying during a period was assumed to have consumed food up to and including the morning of discovery of death.

3.4 Statistics

Statistical evaluation of the results was by means of:

3.4.1 Students 't' test (litter, pup and foetal bodyweights, food consumption, numbers of implantations, numbers of corpora lutea).

3.4.2 Mann-Whitney 'U' test (gestational and lactational bodyweights of dams).



3.4.3 Chi-square test (ratios and proportions).

A value of p of 0.05 or less was taken as the criterion of statistical significance.

4. RESULTS

4.1 Teratology phase

4.1.1 Parent animals

4.1.1.1 Clinical signs/mortalities (Table 1)

Two rats (numbers 20 and 42) from the control and 35 mg/kg ioxynil technical groups respectively, died or were killed during the course of the study. Animal number 20 (control) was found to have littered prematurely on day 20 post-coitum and was killed. The cause of death of animal 42 (35 mg/kg) could not be ascertained due to cannibalism.

There were no observed clinical signs associated with ioxynil technical treatment.

4.1.1.2 Bodyweights (Tables 2 and 3, Figs 1 and 2)

In comparison with the vehicle control animals, the gestational bodyweights of dams with viable young in the 35 mg/kg ioxynil technical group showed a statistically significant reduction ($p < 0.01$) throughout the dosing and post-dosing periods.

Group mean bodyweight gain during the dosing period (days 5-18 post-coitum) was similarly reduced.

4.1.1.3 Food consumption (Tables 4 and 5)

Between days 5 and 8 and 8 and 11 of the dosing period, food consumption (g/rat/day) of animals receiving 35 mg/kg ioxynil technical was statistically significantly reduced ($p < 0.001$ and $p < 0.05$ respectively) when compared with the vehicle control group.

4.1.1.4 Pregnancy rate (Table 7)

The pregnancy rate in the 35 mg/kg ioxynil technical group was lower than that of the control group. However statistical analysis revealed no significant differences in the rates observed.

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4.1.1.5 Litter data (Tables 6 and 7)

4.1.1.5.1 Implantations and pre-implantation loss

The numbers of implantations and pre-implantation losses at 35 mg/kg ioxynil technical were statistically comparable with those of the vehicle control group.

4.1.1.5.2 Litter size and post-implantation loss

The number of viable fetuses per litter and post-implantation losses at 35 mg/kg ioxynil technical were comparable statistically with those of the vehicle controls.

4.1.1.5.3 Foetal weight

A statistically significant reduction ($p < 0.001$) in foetal weight was associated with treatment at 35 mg/kg ioxynil technical.

4.1.1.5.4 Major malformation and minor anomaly (Tables 8, 9 and 24)

Neither the type nor the incidence of major malformation suggested any association with treatment with ioxynil technical. Inter-group differences were not statistically significant.

The only major malformations observed occurred in two pups from litter 30 (35 mg/kg ioxynil technical) which were found to have unilateral right microphthalmia and unilateral right anophthalmia, in comparison with one pup from litter 17 (control) with bilateral microphthalmia.

Minor anomalies were slightly increased in the ioxynil technical group but this increase was not statistically significant when compared with the vehicle control animals.

The numbers of cases of hydronephrosis and supernumerary 14th ribs observed in the ioxynil technical treated litters did show a statistically significant ($p < 0.001$) increase in comparison with the vehicle controls.

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4.2 Littering phase

4.2.1 Parent animals

4.2.1.1 Clinical signs/mortalities (Table 10)

There were no observed reactions associated with ioxynil technical treatment in terms of clinical signs. However there was one death (animal 88, 35 mg/kg ioxynil technical) the cause of which could not be ascertained due to autolytic degeneration.

4.2.1.2 Bodyweights

4.2.1.2.1 Post-coital bodyweights of dams (Tables 11 and 12)

A statistically significant reduction in gestational bodyweight was observed on days 8 and 11 ($p < 0.001$) and days 14 and 18 ($p < 0.05$) post-coitum when compared with the vehicle controls.

Bodyweight gain was statistically significantly reduced ($p < 0.01$) throughout the dosing period at 35 mg/kg ioxynil technical.

4.2.1.2.2 Post-parturition bodyweights of dams (Tables 15 and 16)

Post-parturition bodyweights of ioxynil technical treated dams remained statistically comparable with the vehicle controls throughout lactation.

4.2.1.3 Food consumption (Tables 13 and 14)

Between days 5-8 post-coitum littering phase dams in the 35 mg/kg ioxynil technical group showed a statistically significant ($p < 0.001$) reduction in food consumption. Food consumption after this period (days 8 to 22 post-coitum) remained similar to or showed a statistically significant increase when compared with the vehicle controls.

4.2.1.4 Litter data

4.2.1.4.1 Post-parturition development (Tables 17-22, Fig 3)

The general condition of offspring was unaffected by treatment with ioxynil technical. Litter size at birth, live birth and viability indices, birth weight, bodyweight gain and total litter weight of offspring during the lactation period, and sex ratios at birth and at weaning, were similar in each group.



Figure 3 represents each litters progress for the developmental tests performed. Litters are each represented by a line starting on the day a positive response is first recorded and continuing until 100% occurrence on a litter basis.

No treatment related changes were seen in physical development (pinna unfolding, eye opening, hair growth, tooth eruption, or in surface righting, air righting or startle reflexes) of offspring.

One pup from litter 94 (35 mg/kg ioxynil technical) did not give a full startle in response to 8 kHz pulses throughout the testing period, but did not appear to be 'backward' in any other developmental area.

4.2.1.4.2 Terminal necropsies (Tables 23 and 26)

Terminal necropsies conducted on all weanlings revealed only one abnormality requiring histopathological evaluation. Pup number 11 (dam 74, 35 mg/kg ioxynil technical) was found to have a 1 cm diameter fluid filled mass adhering to tissue around the spleen.

Two pups from litter 75 (35 mg/kg ioxynil technical) were found to have unilateral right anophthalmia.

There were two cases of increased renal pelvic cavitation (Dam 84, pups 1 and 4, 35 mg/kg ioxynil technical).

There were no observed instances of hydroureter in either the control or ioxynil technical treated groups.

4.2.1.5 Skeletal examination (Tables 23-25)

Skeletal examination of all weanlings revealed a statistically significant ($p < 0.001$) increase in the total number of supernumerary 14th rib variants observed for the 35 mg/kg group.

4.2.1.6 Histopathology (Table 26)

Female number 90 (35 mg/kg ioxynil technical) which did not litter was found to have a blood filled mass, approximately 1 cm in diameter, associated with the rectum. Histopathological evaluation revealed a recent haematoma apparently arising in subserosal blood vessels of the rectal wall. The cause of the haematoma could not be determined.

Pup number 11 (dam 74, 35 mg/kg ioxynil technical) was found to have a simple cystic structure lined by flattened epithelium or simple columnar epithelium, and resembling a paraovarian cyst.

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4.2.1.7 Analysis of dosage forms (Appendix V)

Analytical data from the five weekly dosage form preparations revealed the overall mean percentage nominal ioxynil content to be within approximately -3% of that expected (assuming that this batch of technical material has an approximate 88% ioxynil content (see Appendix I)).

Correcting for water and related impurities revealed the overall mean percentage ioxynil technical content of the preparations to be within approximately -3% of that expected.

Homogeneity data were obtained by duplicate analyses of triplicate samples. No significant difference in sample homogeneity was observed. Analysis revealed the samples to be stable under the conditions of storage (-20°C) over a maximum 5 week period (13.2.81 preparation date).

4.2.1.8 Analyses (diet, water and sawdust) (Appendices II and III)

Analytical data on the batch of diet used in this study and a sample of tap water from the source supplying the rats revealed no abnormal results for the contaminants tested (LACDAC 1977).

Analysis of a sample of raw timber used in preparation of the batch of sawdust used in this study also revealed no abnormal findings for the contaminants tested (dieltrin and pentachlorophenol).

5. DISCUSSION

There were only two deaths associated with treatment with 35 mg/kg ioxynil technical, one in each phase of the study and, in the absence of specific lesions, the deaths must be assumed to be compound related.

The maternal observations associated with ioxynil technical treatment at 35 mg/kg in both phases of this study paralleled those seen before (reductions in bodyweight throughout the dosing and post-dosing periods, and reduced food intake during the initial part of the dosing period).

Litter parameters remained essentially unaffected by ioxynil technical treatment except for the reduction in foetal weight which was of a similar order to that seen previously.

The main objects of this study were to confirm the incidence of hydroureter and supernumerary 14th ribs, as seen in a previous ioxynil technical teratogenicity study (Copping, 1981), and assess the effects, if any, on post-parturition development.

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Ioxynil technical administered at 35 mg/kg affected day 22 post-coitum mean foetal weight. Post-parturition mean pup and litter weight, at birth and throughout the weaning period, was higher than in the controls, indicating a very rapid increase in bodyweight gain during the final stage of pregnancy prior to birth.

The incidence of hydroureter associated with 35 mg/kg ioxynil technical treatment during the teratology phase was similar (14%) to that of the previous study (12%). No evidence of hydroureter could be found in pups stillborn, dying during lactation, or in weaned pups of the littering phase.

This increased incidence of hydroureter in day 22 post-coitum rat pups from both studies, although within the range quoted in various background data for this strain of rat, was only associated with treatment at 35 mg/kg ioxynil technical. There was no apparent difference between the controls and animals receiving 5 or 15 mg/kg ioxynil technical (previous study), hence the possibility of this being a spontaneous effect is somewhat remote.

The reduced foetal weight (day 22 post-coitum) observed in the 35 mg/kg ioxynil technical groups from both studies, which may be due to an indirect (maternal toxicity) or a direct effect (foetal toxicity), could have been indicative of impaired foetal development. This possible impairment of foetal development associated with treatment at 35 mg/kg ioxynil technical, although not confirmed skeletally, may have been related to the observed hydroureter.

A lack of co-ordination between the secretory function (timing and volume) of foetal kidneys during intra-uterine life and the transitory changes in ureteral and urethral structure (including late rupture of ureteric membranes) could lead to accumulation of fluid in the ureters (Giroud 1960, Warkany 1971, Monie et al 1957).

This theory is supported by the lack of any observable cases of hydroureter in littering phase animals, and although two cases of unilateral increased renal pelvic cavitation (dam 84 weanlings 1 and 4) were observed, it is thought that these were not indicative of previous hydroureter. The teratology phase showed that approximately 14% of pups at this dosage exhibited some form of hydroureter and for only two pups from the same litter to show increased renal pelvic cavitation, the hydroureter would have to have been particularly severe.

Although this theory is well supported, another possible explanation of the increased incidence of hydroureter in day 22 post-coitum fetuses may be due to a compound induced deficiency, or transitory deficiency in a growth factor, or related substance. Such deficiencies and their effects have been well documented (Monie, Nelson and Evans, 1957) and can cause multiple abnormalities including some similar to those seen in these studies.

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The supernumerary 14th rib variant was assessed for both teratology and littering phases of this study (Tables 23-25).

The % total incidence of supernumerary 14th ribs associated with treatment at 35 mg/kg ioxynil technical was virtually identical between the two phases of this study (teratology 45%, littering 48%) and for that seen in the previous teratology study (40%).

Similarities in the numbers of each type of supernumerary rib combination were also noticed, a reduced bilateral 14th rib accounting for nearly 50% of the total supernumerary 14th rib score.

Considering the dose related incidence of supernumerary 14th ribs observed in the previous teratology study and the confirmatory data obtained from this study, it must be concluded that ioxynil technical does influence the development of supernumerary 14th ribs.

The possession of supernumerary ribs and/or the possible late rupture of ureteric membranes associated with treatment with 35 mg/kg ioxynil technical did not seem to affect the post-parturition development (mortalities, litter size and weight and behavioural testing) when compared to normal (control) animals.

The only major malformations observed during either phase of the study at 35 mg/kg ioxynil technical were 3 cases of anophthalmia and 1 of microphthalmia, these occurring in two litters. A single case of microphthalmia was observed in a control animal.

No similar observations were made in the previous teratology study and as rats of this strain do show a high incidence of this type of abnormality it was thought that this was not treatment associated.

6. CONCLUSION

The data from both studies support the view that although ioxynil technical does seem to exert either a direct or indirect effect, causing increased hydroureter in day 22 post-coitum fetuses, there is little or no evidence of the continuance of this abnormality after birth.

This transitory hydroureter and the possession of supernumerary 14th ribs has no apparent effect upon post-parturition development to weaning in the CD rat.

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Table 1
 Ioxynil technical : Teratogenicity study with littering phase,
 by the oral route in the rat

Clinical signs/mortalities of teratology phase animals

Treatment group	Animal number	Day post-coitum	Observation	Pregnant Y/N
0 mg/kg	20	20	Killed - found to be littering prematurely	Y
35 mg/kg	42	10	Found dead - Unable to determine cause of death due to cannibalism. No pregnancy data available.	

Y = pregnant
 N = non-pregnant

0.4

0.4

0.4

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Table 2.1

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat

Control : Individual bodyweights of teratology phase dams

Animal number	Bodyweights (g) on days <u>post-coitum</u>					
	5	8	11	14	18	22
1	226	239	255	274	313	352
2	209	221	236	249	287	317
3	231	245	267	283	321	362
4	223	243	263	280	328	368
5	208	221	247	264	301	344
6	206	219	235	251	290	324
7	212	229	249	263	299	340
8	229	245	267	284	334	376
9	220	241	265	286	322	332
10	216	235	256	276	312	336
11	233	261	279	303	350	379
12	212	234	249	271	300	346
15	230	254	274	299	331	394
16	209	228	252	274	308	347
17	245	273	294	320	347	397
18	226	251	267	301	332	405
19	214	234	250	277	303	337
21	216	235	252	269	298	344
22	225	242	255	283	315	368
24	235	255	268	297	326	369
LITTERED						
20	Animal littered prematurely on day 20 <u>post-coitum</u> . Bodyweight data excluded from group means.					
NON-PREGNANT						
13						
14						
23						

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Table 2.2

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat

Ioxynil technical 35 mg/kg : Individual bodyweights of teratology phase dams

Animal number	Bodyweights (g) on days post-coitum					
	5	8	11	14	18	22
25	246	233	244	261	312	340
26	227	230	236	242	271	304
27	209	199	215	222	273	302
28	213	207	214	222	279	298
29	241	240	256	272	312	361
30	226	219	223	227	270	309
31	225	226	246	252	310	348
32	208	207	209	215	266	316
34	230	238	238	258	300	340
35	217	192	225	246	286	335
38	230	226	246	265	292	339
43	206	202	215	242	273	324
45	219	215	240	265	263	323
46	225	227	235	258	257	297
47	230	234	254	281	292	354
48	221	226	245	269	277	343
DIED						
42						
NON-PREGNANT						
33						
36						
37						
39						
40						
41						
44						

Table 3.1

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat

Group mean bodyweights of teratology phase dams with viable young

Treatment Group	Number of animals	Group mean bodyweight (g) on days <u>post-coitum</u>					
		5	8	11	14	18	22
Control	20	221 (2)	240 (3)	259 (3)	280 (4)	316 (4)	357 (6)
Ioxynil technical 35 mg/kg	16	223 (3)	** 220 (4)	** 234 (4)	** 250 (5)	** 283 (4)	** 327 (5)

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Standard error in parenthesis

** p<0.01

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Table 3.2

Ioxynil technical : Teratogenicity study with littering phase,
by the oral route, in the rat

Group mean bodyweight gain (g) days 5-22 post-coitum of
teratology phase dams with viable young

Treatment Group	Number of animals	Group mean bodyweight gain (g) days 5-22 post-coitum				
		5-8	5-11	5-14	†5-18	5-22
Control	20	19	38	59	95	136
Ioxynil technical 35 mg/kg	16	-3	11	27	**60	104

* p<0.01

† statistical analysis conducted for dosing period only (days 5-18 post-coitum)

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Table 4.1

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat

Control : Individual food consumption of teratology phase dams

Cage No.	Animal No.	g/rat/day for days <u>post-coitum</u>					
		†1-5	5-8	8-11	11-14	14-18	18-22
1	1-4	25	27	27	27	32	24
2	5-8	25	26	26	27	31	25
3	9-12	22	26	24	27	28	22
4	13-16	22	25	24	26	27	26
5	17-20	23	28	25	35	29	29
6	21-24	24	26	25	29	27	26

† Animals were obtained on various days post-coitum hence figure represents food consumption over a 1, 2, 3 or 4 day period.

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Table 4.2

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat

Ioxynil technical 35 mg/kg : Individual food consumption of teratology phase dams

Animal No. Cage No.	g/rat/day for days post-coitum					
	†1-5	5-8	8-11	11-14	14-18	18-22
7 25-28	25	21	23	27	36	23
8 29-32	23	21	24	28	36	27
9 33-36	21	19	23	27	29	27
10 37-40	23	22	21	26	27	27
11 41-44	23	22	20	31	28	27
12 45-48	23	24	26	38	29	32

† Animals were obtained on various days post-coitum hence figure represents food consumption over a 1, 2, 3 or 4 day period.

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Table 5

Ioxynil technical : Teratogenicity study with littering phase,
by the oral route, in the rat

Group mean food consumption of teratology phase dams

Group \ Day No.	g/rat/day for days post-coitum					
	†1-5	5-8	8-11	11-14	14-18	18-22
Control	23.5	26.3	25.2	28.5	29.0	25.3
35 mg/kg ioxynil technical	23.0	*** 21.5	* 22.8	29.5	30.8	27.2

* p<0.05

*** p<0.001

† Animals were obtained on various days post-coitum hence figure represents food consumption over a 1, 2, 3 or 4 day period.

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Table 6.1
Toxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat
Control : Individual litter data (teratology phase)

Animal No.	Corpora Lutea	Total Implantations	Pre-implantation loss %	Live Fetuses		Uterine Deaths			Post-implantation loss %	Remarks	
				No. ♂ / ♀	Mean wt (g) A	Early	Late	Total			
1	14	13	7	11	7/4	5.9	2	0	2	15	
2	13	12	8	12	7/5	5.2	0	0	0	0	
3	13	11	15	11	6/5	5.8	0	0	0	0	
4	15	13	13	12	4/8	5.8	1	0	1	8	
5	10	10	0	10	6/4	5.5	0	0	0	0	
6	12	12	0	12	5/7	5.0	0	0	0	0	
7	13	10	23	9	5/4	5.3	1	0	1	10	
8	15	11	27	11	5/6	5.4	0	0	0	0	
9	15	14	7	14	10/4	5.1	0	0	0	0	
10	15	12	20	12	7/5	5.2	0	0	0	0	
11	15	14	7	11	8/3	5.7	3	0	3	21	
12	10	6	40	6	3/3	5.8	0	0	0	0	
15	18	13	28	5	2/3	5.7	8	0	8	62	
16	13	12	8	11	5/6	5.4	1	0	1	8	
17	14	14	0	14	7/7	5.3	0	0	0	0	
18	14	12	14	12	6/6	5.8	0	0	0	0	
19	18	12	33	12	4/8	4.9	0	0	0	0	
20											Animal littered prematurely on day 20 post-coitum
21	-13	9†	31	7	5/2	6.6	†2	0	2	22	† includes one perivital implantation (early death)
22	17	12	0	12	4/8	5.6	0	0	0	0	
24	10	7	30	7	2/5	5.8	0	0	0	0	
13			13								No visible implantations in uterus
14											No visible implantations in uterus
23											No visible implantations in uterus

Table 6.2
Loxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat
Loxynil technical 35 mg/kg : Individual litter data (teratology phase)

Animal No.	Corpora Lutea	Total implantations	Pro-implantation Loss %	Live Fetuses		Uterine Deaths			Post-implantation Loss %	Remarks	
				No. ♂ / ♀	Mean wt (g) A	Early	Late	Total			
25	17	15	12	15	5/10	4.7	0	0	0	0	
26	11	7	36	4	1/3	4.8	3	0	3	43	
27	14	13	7	11	8/3	4.6	2	0	2	15	
28	16	13	19	12	1/11	4.2	1	0	1	8	
29	13	12	8	12	8/4	5.1	0	0	0	0	
30	9	7	22	7	4/3	5.1	0	0	0	0	
31	16	15	6	14	7/7	4.8	0	1	1	7	
32	13	11	15	10	3/7	5.0	1	0	1	9	
34	11	10	9	10	5/5	5.1	0	0	0	0	
35	14	13	7	12	4/8	4.6	1	0	1	8	
38	11	5	55	5	2/3	5.9	0	0	0	0	No implantations visible in left uterine horn
43	11	11	0	10	5/5	5.4	1	0	1	9	
45	11	11	0	10	5/5	5.6	1	0	1	9	
46	15	12	20	11	10/1	4.4	1	0	1	8	
47	14	13	7	12	4/8	5.0	1	0	1	8	
48	16	12	25	12	8/4	4.8	0	0	0	0	
33											No visible implantations in utero
36											No visible implantations in utero
37											No visible implantations in utero
39											No visible implantations in utero
40											No visible implantations in utero
41											No visible implantations in utero
44											No visible implantations in utero

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Table 7
Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat
Group mean litter data (teratology phase)

Group	No. of animals per group	No. pregnant	No. of litters used in statistical analyses	Corpora lutea mean no./animal	Implantations mean no./animal	Mean pre-implantation loss/animal % (B)	Live (ortuses				Uterine deaths		Mean post-implantation loss/animal % (B)			
							Total no.	Mean no./animal	No. males	No. females	d/p	Mean wt. (g) (B)		Total no.	Early deaths	Late deaths
Control	24	21	† 20	13.6 (0.5)	11.5 (0.5)	15.6	211	10.6 (0.6)	108	103	1.0	5.5	18	18	0	7.3
Ioxynil technical 35 mg/kg	24	16	16	13.3 (0.6)	11.3 (0.7)	15.5	167	10.4 (0.7)	60	87	0.9	4.9	13	12	1	7.8

Standard error in parenthesis

† excludes data from dam 20 due to premature littering on day 20 post-coitum

B = Method B

*** p<0.001

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Table 8.1

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat

Control : Foetal examination (major malformation and minor anomaly)

Female number	Number of young				
	No. in litter	Major malformation		Minor anomaly	
		No.	Description	No.	Description
1	11 (A)	0		1	Increased size of anterior fontanelle.
				1	Bilateral haemorrhagic kidneys.
2	12	0		1	Absent ossification, proximal phalanges in left forepaw.
3	11 (B)	0		0	
4	12	0		1	13th thoracic vertebral centrum bipartite.
				1	11th thoracic vertebral centrum bipartite.
5	10	0		1	Absent ossification 5th sternebra.
6	12	0		1	12th thoracic vertebral centrum bipartite.
				1	Absent ossification, proximal phalanges in each forepaw.
7	9	0		0	
8	11	0		0	
9	14	0		1	Right 13th rib reduced to half normal length.
				1	Right 13th rib reduced to one third normal length.

(A) 1 pup : processing damage to left thoracic region causing damage to 6th-13th ribs
 (B) 1 pup : mutilated below 6th thoracic vertebral centrum. Hind limbs skeletally normal

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Table 9.1 (continued)

Ioxynil technical : Teratogenicity study with littering phase,
by the oral route, in the rat

Control : Foetal examination (major malformation and minor anomaly)

Female number	Number of young				
	No. in litter	Major malformation		Minor anomaly	
		No.	Description	No.	Description
10	12 [†]	0		1	6th-11th ribs on right and 7th-10th ribs on left thickened near capitulae.
				1	Absent ossification proximal phalanges in each forepaw.
11	11	0		1	1st-13th ribs on right thickened near capitulae. Absent ossification, proximal phalanges in each forepaw.
				1	12th thoracic vertebral centrum bipartite.
				1	6th-13th ribs on right and 9th-13th ribs on left thickened near capitulae.
				1	6th thoracic vertebral centrum bipartite.
				1	13th thoracic vertebral centrum bipartite.
				1	11th thoracic vertebral centrum bipartite.
12	6	0		1	Bilateral hydroureter.
15	5	0		1	5th sternebra absent ossification.
16	11	0		1	Absent ossification proximal phalanges in left forepaw.

[†] Only 11 pups found at skeletal examination

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Table 3.1 (continued)

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat

Control : Foetal examination (major malformation and minor anomaly)

Female number	Number of young				
	No. in litter	Major malformation		Minor anomaly	
		No.	Description	No.	Description
17	14	1	Bilateral microphthalmia.	1	Absent ossification, proximal phalanges in each forepaw.
				1	11th thoracic vertebral centrum bipartite.
18	12	0		1	Absent ossification, proximal phalanges in each forepaw.
19	12	0		1	5th sternebra absent ossification.
21	7	0		0	
22	12 (C)	0		1	13th ribs reduced.
24	7 (D)	0		1	Absent ossification of proximal phalanges in each forepaw. Left iris blood suffused.
				1	11th thoracic vertebral centrum bipartite.

(C) 1 pup : 4th thoracic vertebral centrum damaged during dissection

(D) 1 pup : 6th rib on left absent due to processing error

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Table 8.2

Ioxynil technical : Teratogenicity study with littering by the oral route, in the rat

35 mg/kg ioxynil technical : Foetal examination (major malformation and minor anomaly)

Female number	Number of young				
	No. in litter	Major malformation		Minor anomaly	
		No.	Description	No.	Description
25	15	0		1	Bilateral hydroureter.
26	4	0		1	Absent ossification, proximal phalanges in each forepaw. Only 3 metacarpals ossified in each forepaw.
				1	Absent ossification, proximal phalanges in each forepaw.
27	11	0		0	
28	12	0		3	Absent ossification, proximal phalanges in each forepaw.
				1	Bilateral hydroureter. Absent ossification, proximal phalanges in each forepaw.
				1	Bilateral haemorrhagic kidneys. Absent ossification, proximal phalanges in each forepaw.
				2	Absent ossification, proximal phalanges in each forepaw. Only 3 metacarpals ossified in each forepaw.
29	12	0		†1	Bilateral hydroureter.
				1	Bilateral hydroureter.

† No correlation can be made between this malformation and any subsequent skeletal findings as individual foetal identification became detached during processing.

(E) 6th and 7th ribs on right absent due to processing error

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Table 8.2 (continued)

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat

35 mg/kg ioxynil technical : Foetal examination (major malformation and minor anomaly)

Female number	Number of young				
	No. in litter	Major malformation		Minor anomaly	
		No.	Description	No.	Description
30	7	1	Unilateral right microphthalmia, orbit reduced.		Bilateral hydroureter.
		1	Unilateral right anophthalmia, orbit reduced.		2nd thoracic vertebral centrum bipartite.
				1	Bilateral hydroureter. Bilateral haemorrhagic kidneys.
				1	Bilateral hydroureter.
31	14	0		0	
32	10 (F)	0		1	Right carotid artery malpositioned.
34	10 ^{††}	0		1	Bilateral hydroureter.
35	12	0		2	Bilateral haemorrhagic kidneys.
				1	5th sternebra absent ossification.
38	5	0		4	Bilateral hydroureter.
43	10	0		2	Bilateral hydroureter.
45	10	0		2	Bilateral hydroureter.

†† 11 pups found at skeletal examination.

(F) 11th, 12th, 13th ribs on right absent due to processing error.

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Table 8.2 (continued)

Ioxynil technical : Teratogenicity study with littering phase,
by the oral route, in the rat

35 mg/kg ioxynil technical : Foetal examination (major malformation and minor anomaly)

Female number	Number of young					
	No. in litter	Major malformation		Minor anomaly		No.
		No.	Description	No.	Description	
46	11	0		4	Bilateral hydrourerter	
				1	Bilateral hydrourerter.	
				1	Bilateral haemorrhagic kidneys.	
					Absent ossification, proximal phalanges in each forepaw.	
47	12	0		0		
48	12	0		3	Bilateral hydrourerter.	

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Table 9

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat

Foetal examination (major malformation and minor anomaly)

Summary of Table 8

Treatment Group	No. skeletons examined	No. litters examined	Number of young			
			Major malformation		Minor anomaly [†]	
			Total number	Mean % (C)	Total number	Mean % (C)
Control	210	20	1	0.36	28	13.45
Ioxynil technical 35 mg/kg	168	16	2	1.79	36	25.30

† young showing major malformations excluded

C = Method C

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Table 10
 Ioxynil technical : Teratogenicity study with littering phase, by the oral route in the rat
Clinical signs/mortalities of littering phase animals

Treatment group	Animal number	Day post-coitum	Observation	Pregnant Y/N
35 mg/kg	88	18	Found dead. Cause of death not ascertained. No pregnancy data available.	
35 mg/kg	90	Animal failed to litter	Blood filled mass approximately 1 cm in diameter adhering externally to the rectum.	N
35 mg/kg	97	Animal failed to litter	Hydrometra.	N

Y = pregnant
 N = non-pregnant

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Table 11.1

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat

Control : Individual (post-coital) bodyweights of littering phase dams

Animal number	Bodyweights (g) on days post-coitum					
	5	8	11	14	18	22
49	218	243	260	282	320	340
50	206	212	230	256	287	326
51	217	225	247	274	305	363
52	221	236	254	278	309	367
53	212	227	235	253	283	333
54	203	212	222	243	269	317
55	213	221	241	261	299	346
56	213	229	244	264	288	312
57	228	243	267	302	338	373
58	226	241	255	276	299	340
59	221	243	263	287	321	364
60	208	226	237	261	301	359
61	208	228	247	273	312	345
63	212	222	239	256	286	310
64	202	214	229	253	288	309
66	211	222	243	260	287	321
67	213	233	258	274	308	367
69	204	218	235	250	267	292
70	236	257	279	313	351	380
71	228	242	267	287	341	381
72	205	217	233	251	285	315
73	214	230	250	273	310	326
NON-PREGNANT						
62						
65						
68						

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Table 11.2

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat

- Ioxynil technical 35 mg/kg : Individual (post-coital) bodyweights of littering phase dams

Animal number	Bodyweights (g) on days post-coitum					
	5	8	11	14	18	22
74	215	200	224	253	294	361
75	233	216	234	262	284	341
76	220	201	222	254	282	346
77	210	195	208	234	261	316
78	216	218	241	266	299	362
79	218	206	221	250	277	317
80	224	219	238	267	303	357
81	203	202	222	243	272	328
82	207	207	235	262	300	341
83	203	215	235	259	302	348
84	233	232	249	272	300	348
85	194	192	210	229	264	317
86	216	206	219	237	277	309
87	208	205	234	257	294	350
91	205	204	215	237	262	289
92	203	217	238	260	293	314
94	210	217	240	259	291	334
95	212	226	246	263	299	353
98	223	210	233	260	288	326
DEAD						
88	207	204	215	248	Found dead day 18	
NON PREGNANT						
89						
90						
93						
96						
97						

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Table 12.1

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat

Group mean (post-coital) bodyweights of littering phase dams with viable young

Treatment Group	Number of animals	Group mean bodyweight (g) on days post-coitum					
		5	8	11	14	18	22
Control	22	215 (2)	229 (3)	247 (3)	269 (4)	302 (5)	340 (6)
Ioxynil technical 35 mg/kg	19	214 (2)	*** 210 (2)	*** 230 (3)	* 254 (3)	* 286 (3)	335 (5)

Standard error in parenthesis

* p<0.05

*** p<0.001

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Table 12.2

Ioxynil technical : Teratogenicity study with littering phase,
 by the oral route, in the rat
Group mean (post-coital) bodyweight gain (g) of littering phase dams
with viable young days 5-22 post-coitum

Treatment Group	Number of animals	Group mean bodyweight gain (g) days 5-22 post-coitum				
		5-8	5-11	5-14	†5-18	5-22
Control	22	14	32	54	87	125
Ioxynil technical 35 mg/kg	19	-4	16	40	**72	121

** p<0.01

† statistical analysis performed

LB

R.Tox.89

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Table 13.1

Ioxynil technical : Teratogenicity study with littering phase,
by the oral route, in the rat

Control : Food consumption of littering phase dams

with viable young

Day No. Rat No.	g/rat/day for days <u>post-coitum</u>					
	† 1-5	5-8	8-11	11-14	14-18	18-22
49	22	29	27	31	27	19
50	21	24	24	27	24	21
51	20	27	29	31	29	28
52	21	27	27	28	29	26
53	23	26	24	25	25	23
54	21	22	22	24	22	23
55	23	25	26	27	27	27
56	27	28	28	30	26	29
57	27	31	33	37	31	26
58	28	28	28	29	25	25
59	22	28	29	32	28	30
60	28	29	29	30	29	27
61	21	27	27	29	27	23
63	24	24	26	25	22	18
64	18	28	26	29	28	21
66	25	26	30	23	27	24
67	21	25	26	27	27	28
69	20	25	25	27	23	15
70	28	32	35	39	34	26
71	26	28	30	30	32	27
72	22	24	25	26	28	23
73	20	28	29	32	30	20

† Animals were obtained on various days post-coitum hence
figure represents food consumption over a 1,2,3 or 4 day period.

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Table 13.2

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat

Ioxynil technical 35 mg/kg : Food consumption of littering phase dams with viable young

Rat No.	Day No.	g/rat/day for days post-coitum					
		†1-5	5-8	8-11	11-14	14-18	18-22
74		18	19	27	24	31	31
75		20	18	24	33	29	31
76		21	19	23	35	29	35
77		17	18	18	29	29	32
78		24	24	30	35	30	32
79		18	16	26	32	31	29
80		20	23	28	35	34	32
81		15	22	25	30	28	31
82		18	22	28	33	30	26
83		23	22	27	30	29	30
84		27	23	26	34	31	29
85		21	19	25	29	28	26
86		28	15	20	30	31	26
87		24	19	32	31	31	32
91		24	22	29	26	27	26
92		23	23	34	23	28	23
94		23	22	27	30	29	30
95		24	26	30	34	30	31
98		27	19	30	34	29	27

† Animals were obtained on various days post-coitum hence figure represents food consumption over a 1, 2, 3 or 4 day period.

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Table 14

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat

Group mean food consumption of littering phase dams

Day No. / Group	g/rat/day for days <u>post-coitum</u>					
	†1-5	5-8	8-11	11-14	14-18	18-22
Control	23	27	28	29	27	24
35 mg/kg ioxynil technical	22	***21	27	* 31	** 30	***29

* p<0.05

** p<0.01

*** p<0.001

† Animals were obtained on various days post-coitum hence figure represents food consumption over a 1, 2, 3 or 4 day period.

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Table 15.1

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat

Control : Individual post-partum bodyweights of littering phase dams

Animal number	Bodyweights (g) on days <u>post-partum</u>					
	0	4	8	12	16	21
49	264	286	304	332	347	322
50	244	253	276	289	293	265
51	†261	279	293	290	310	296
52	†270	273	290	304	322	314
53	†261	289	266	287	298	258
54	248	249	272	285	286	271
55	274	282	290	315	324	264
††56	(279)	(n.r.)	(270)	(282)	(291)	(n.r.)
57	283	306	343	357	355	337
58	†271	283	296	297	304	297
59	†286	296	306	334	338	316
60	269	273	289	281	305	283
61	266	278	277	309	341	273
63	†216	245	271	291	296	281
64	227	239	260	291	314	307
66	245	260	286	294	311	293
67	†263	276	287	317	339	322
69	†199	232	272	291	303	263
70	304	334	325	347	354	322
71	274	306	331	336	344	333
72	206	234	268	273	282	277
73	226	269	308	320	351	315

n.r. no record

† day 1 post-partum

†† All pups missing on day 2 post-partum. Dam excluded from group mean bodyweight calculation

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Table 15.2

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat

Ioxynil technical 35 mg/kg : Individual post-partum bodyweights of littering phase dams

Animal number	Bodyweights (g) on days post-partum					
	0	4	8	12	16	21
74	255	275	307	305	305	305
75	†238	263	287	317	328	297
76	†246	279	282	304	315	295
77	247	264	296	296	323	278
78	†274	294	315	316	329	296
79	270	268	290	305	316	317
80	276	289	303	328	321	291
81	246	252	279	313	336	285
82	236	271	297	331	317	304
83	260	281	283	317	312	287
84	263	280	291	307	316	299
85	239	241	260	281	272	254
86	241	250	267	301	295	282
87	246	269	289	311	335	297
91	234	245	252	263	285	260
92	221	254	284	313	327	305
94	241	276	302	314	313	293
95	267	292	326	337	336	291
98	214	257	292	313	328	272

† day 1 post-partum

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Table 16

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat

Group mean post-partum bodyweights of littering phase dams with viable young

Treatment Group	Number of animals	Group mean bodyweight (g) on days post-partum					
		0	4	8	12	16	21
Control	21†	255 (6)	272 (5)	291 (5)	307 (5)	320 (5)	296 (6)
Ioxynil technical 35 mg/kg	19	248 (4)	268 (4)	290 (4)	309 (4)	316 (4)	290 (4)

Standard error in parenthesis

† Excludes data from dam 56

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Table 17.1

Ioxynil technical : Teratogenicity study with littering phase,
by the oral route, in the rat

Control : Mean pup bodyweights (g)(littering phase)

Animal number	Mean pup bodyweights on days post-partum					
	0	4	8	12	16	21
49	5.3	9.1	13.1	18.9	26.1	38.1
50	5.5	8.2	13.6	20.9	28.2	39.0
51	†6.2	9.6	15.4	22.0	30.5	41.1
52	†6.6	11.8	20.4	32.3	43.4	62.9
53	†6.7	10.5	15.7	22.1	30.1	41.6
54	5.6	8.8	13.3	22.2	29.6	36.1
55	5.8	9.6	15.1	22.0	32.2	37.4
††56	(8.0)	-	-	-	-	-
57	6.0	10.0	15.7	22.9	30.3	45.3
58	†6.4	10.6	16.9	24.2	32.9	46.9
59	†6.4	9.9	16.9	24.2	32.9	44.6
60	5.5	7.8	10.6	15.9	20.8	26.1
61	6.2	10.7	17.2	24.1	31.6	43.2
63	†5.6	8.4	14.7	22.4	28.6	39.2
64	5.8	7.9	13.6	21.3	29.6	43.2
66	6.2	10.8	16.3	22.9	30.1	41.1
67	†5.7	8.1	14.0	22.0	31.0	43.8
69	†6.5	9.4	15.9	23.9	31.0	40.6
70	5.4	8.3	13.6	20.5	27.7	36.6
71	6.0	10.1	15.9	23.7	30.6	45.1
72	5.9	10.3	17.5	23.7	29.9	47.7
73	5.5	10.4	16.9	24.5	32.2	48.9

† day 1 post-partum

†† All pups missing on day 2 post-partum, data not included in group mean pup bodyweight calculations

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Table 17.2

Ioxynil technical : Teratogenicity study with littering phase,
 by the oral route, in the rat

Ioxynil technical 35 mg/kg : Mean pup bodyweights (g)(littering phase)

Animal number	Mean pup bodyweights on days post-partum					
	0	4	8	12	16	21
74	6.5	11.5	15.8	23.3	30.7	44.0
75	†6.4	9.6	15.5	22.9	31.3	43.8
76	†5.9	8.3	14.1	21.6	29.2	37.2
77	7.0	11.8	17.2	25.2	32.5	49.5
78	†5.5	6.9	11.1	17.1	23.4	30.1
79	6.0	9.8	15.3	23.6	33.7	49.1
80	6.1	12.1	19.2	26.9	36.8	53.2
81	6.4	10.1	15.3	21.7	29.6	41.4
82	5.7	9.6	15.8	23.0	31.3	46.1
83	5.6	9.0	13.7	19.9	26.2	33.7
84	6.6	10.3	17.8	24.1	32.7	43.0
85	5.5	9.4	14.3	21.3	28.7	39.0
86	5.7	9.3	14.8	22.1	28.5	40.5
87	5.9	9.7	15.6	22.9	30.6	37.8
91	6.2	11.1	17.9	25.6	33.7	45.3
92	5.7	9.2	14.1	20.9	29.3	40.6
94	7.4	12.8	19.2	27.9	38.3	51.1
95	7.0	13.1	19.3	27.7	37.5	51.1
98	6.1	11.3	19.1	27.4	35.7	48.1

† day 1 post-partum

Table 18

Ioxynil technical : Teratogenicity study with littering phase,
 by the oral route, in the rat

Group mean pup weight (g)

Group	Number of litters	Day post-partum					
		0	4	8	12	16	21
Control	† 21	5.9	9.5	15.4	22.7	30.4	42.3
Ioxynil technical 35 mg/kg	19	6.2	10.3	16.1	23.4	31.6	43.4

† Excludes data from litter 56

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Table 19.1

Ioxynil technical : Teratogenicity study with littering phase,
by the oral route, in the rat

Control : Individual litter weights

Animal number	Litter weights (g) on days <u>post-partum</u>					
	0	4	8	12	16	21
49	69.0	117.8	170.1	246.0	339.9	495.4
50	72.0	107.0	176.6	271.5	366.7	506.6
51	†73.9	115.1	169.8	242.3	335.4	452.4
52	†33.0	59.2	102.2	161.3	217.1	314.5
53	†60.4	94.7	141.6	198.6	270.9	374.2
54	55.7	87.6	137.6	221.5	296.0	361.3
55	58.1	86.3	135.6	197.9	289.9	336.6
†† 56	(23.9)	-	-	-	-	-
57	78.6	129.9	204.0	298.3	393.9	588.4
58	†50.9	84.8	135.4	193.2	262.9	375.3
59	†51.5	79.1	134.8	193.5	263.2	356.4
60	77.2	109.4	148.0	222.3	291.3	365.1
61	68.6	107.1	172.0	241.0	316.4	432.4
63	†67.5	100.8	176.3	268.3	343.1	470.5
64	52.1	63.4	108.7	170.6	236.7	345.9
66	62.2	108.0	163.4	229.3	301.2	410.6
67	†63.0	72.7	126.2	198.0	279.0	394.5
69	†78.4	113.3	190.8	286.2	372.1	486.9
70	64.5	99.7	163.1	245.9	332.7	439.4
71	77.9	130.8	207.2	307.9	398.0	585.7
72	65.4	102.9	174.8	236.5	298.6	477.4
73	60.9	114.8	185.4	269.9	353.7	538.3

† day 1 post-partum

†† All pups missing on day 2 post-partum, data not included in group mean litter weight calculations

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Table 19.2

Ioxynil technical : Teratogenicity study with littering phase,
by the oral route, in the rat

Ioxynil technical 35 mg/kg : Individual litter weights

Animal number	Litter weights (g) on days <u>post-partum</u>					
	0	4	8	12	16	21
74	78.1	137.4	190.1	279.7	368.2	527.5
75	†76.8	115.0	186.2	274.6	375.2	525.6
76	†65.2	91.5	155.5	237.5	321.4	409.2
77	70.2	117.8	171.6	252.2	325.0	494.7
78	†76.6	96.3	155.4	238.7	327.9	421.4
79	47.7	78.6	122.0	188.7	270.1	393.0
80	48.5	96.5	153.4	215.1	294.3	425.3
81	70.9	111.4	168.2	238.6	325.5	454.9
82	62.7	105.7	173.3	253.1	343.8	507.2
83	72.9	117.4	177.6	259.2	340.5	438.2
84	66.3	103.4	177.8	241.1	326.6	429.7
85	65.8	112.7	157.5	234.3	316.2	429.0
86	57.3	93.0	147.7	221.2	285.1	405.0
87	58.7	87.3	140.5	206.1	275.0	339.9
91	37.4	55.3	89.4	128.2	168.4	226.7
92	62.6	101.2	155.4	230.4	321.8	446.2
94	74.4	127.6	192.2	278.9	383.1	511.0
95	70.1	130.6	192.9	277.1	374.6	511.2
98	67.4	124.7	210.6	301.5	392.5	528.6

† day 1 post-partum

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Table 20

Ioxynil technical : Teratogenicity study with littering phase,
 by the oral route, in the rat

Group mean litter weight (g)

Group	Number of litters	Day post-partum					
		0	4	8	12	16	21
Control	†21	63.8	99.3	158.3	233.3	312.3	433.7
Ioxynil technical 35 mg/kg	19	64.7	105.4	164.1	239.8	322.9	443.4

† Excludes data from litter 56

Table 21.1

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat

Control : Post-parturition litter data

Female number	Number born	Number live day 0		Number live day 1 (24 hours)	Number live day 4		Number live day 8		Number live day 12		Number live day 16		Number live day 21			
		♂	♀		♂	♀	Total	♂	♀	Total	♂	♀	Total	♂	♀	Total
49	13	5	8	13	5	8	13	5	8	13	5	8	13	5	8	13
††50	13	8	5	13	8	5	13	6	7	13	6	7	13	6	7	13
51	12	†7	5	12	7	4	11	7	4	11	7	4	11	7	4	11
‡2	†3	2	5	5	3	2	5	3	2	5	3	2	5	3	2	5
††53	9	†5	4	9	5	4	9	4	5	9	4	5	9	4	5	9
54	10	3	7	10	3	7	10	3	7	10	3	7	10	3	7	10
55	10	7	3	10	6	3	9	6	3	9	6	3	9	6	3	9
††56	(3)	(0)	(3)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
57	13	9	4	13	9	4	13	9	4	13	9	4	13	9	4	13
58	8	†4	4	8	4	4	8	4	4	8	4	4	8	4	4	8
59	8	†3	5	8	3	5	8	3	5	8	3	5	8	3	5	8
60	14	10	4	14	10	4	14	10	4	14	10	4	14	10	4	14
61	11	4	7	11	3	7	10	3	7	10	3	7	10	3	7	10
63	12	†5	7	12	5	7	12	5	7	12	5	7	12	5	7	12
64	11 [†]	5	4	9	4	4	8	4	4	8	4	4	8	4	4	8
66	10	3	7	10	3	7	10	3	7	10	3	7	10	3	7	10
67	12	†8	3	11	6	3	9	6	3	9	6	3	9	6	3	9
69	12	†8	4	12	8	4	12	8	4	12	8	4	12	8	4	12
70	12	3	9	12	3	9	12	3	9	12	3	9	12	3	9	12
71	13	7	6	13	7	6	13	7	6	13	7	6	13	7	6	13
72	11	4	7	11	4	6	10	4	6	10	4	6	10	4	6	10
73	12	8	3	11	8	3	11	8	3	11	8	3	11	8	3	11

† day 1 post-partum
 †† sexes on days 0, 4 and 8 incorrect
 ††† All pups missing on day 2 post-partum, data not included in group mean calculations (dam not lactating)
 ‡ includes one pup extensively mutilated - unable to determine whether or not stillborn.
 # one pup killed on humane grounds due to cannibalism

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Table 21.2

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat
Ioxynil technical 35 mg/kg : Post-parturition litter data

Female number	Number born	Number live day 0			Number live day 1 (24 hours)	Number live day 4			Number live day 8			Number live day 12			Number live day 16			Number live day 21		
		♂	♀	Total		♂	♀	Total	♂	♀	Total	♂	♀	Total	♂	♀	Total	♂	♀	Total
74	12	7	5	12		7	5	12	7	5	12	7	5	12	7	5	12	7	5	12
75	12	† 6	6	12		6	6	12	6	6	12	6	6	12	6	6	12	6	6	12
76	11	† 7	4	11		7	4	11	7	4	11	7	4	11	7	4	11	7	4	11
77	10	4	6	10		4	6	10	4	6	10	4	6	10	4	6	10	4	6	10
78	14	† 6	8	14		6	8	14	6	8	14	6	8	14	6	8	14	6	8	14
79	8	1	7	8		1	7	8	1	7	8	1	7	8	1	7	8	1	7	8
80	9	2	6	8		2	6	8	2	6	8	2	6	8	2	6	8	2	6	8
† 81	11	6	5	11		5	6	11	5	6	11	5	6	11	5	6	11	5	6	11
82	11	4	7	11		4	7	11	4	7	11	4	7	11	4	7	11	4	7	11
83	13	6	7	13		6	7	13	6	7	13	6	7	13	6	7	13	6	7	13
84	10	4	6	10		4	6	10	4	6	10	4	6	10	4	6	10	4	6	10
85	12	3	9	12		3	8	11	3	8	11	3	8	11	3	8	11	3	8	11
86	10	6	4	10		6	4	10	6	4	10	6	4	10	6	4	10	6	4	10
87	11	6	4	10		5	4	9	5	4	9	5	4	9	5	4	9	5	4	9
91	6	5	1	6		5	0	5	5	0	5	5	0	5	5	0	5	5	0	5
92	11	8	3	11		8	3	11	8	3	11	8	3	11	8	3	11	8	3	11
94	10	5	5	10		5	5	10	5	5	10	5	5	10	5	5	10	5	5	10
† 95	10	3	7	10		2	8	10	2	8	10	2	8	10	2	8	10	2	8	10
98	11	4	7	11		4	7	11	4	7	11	4	7	11	4	7	11	4	7	11

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† day 1 post-partum
 † sex on day 0 incorrect

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Table 22
Ioxynil technical : Teratogenicity study with littering phase,
by the oral route, in the rat

Group mean live birth, viability and lactation indices

Group	Live birth index (%)	Viability indices (%) on day post-partum					Lactation index
		4	8	12	16	21	
Control	95	100	99	99	99	99	99.5
Ioxynil technical 35 mg/kg	98	99	99	99	99	99	100

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Table 23.1
Toxynil technical : Tetagenicity study with littering phase, by the oral route, in the rat
Control : Weanling observations : Terminal necropsy and incidence of supernumerary 14th ribs

Dam No.	No. of pups in litter at weaning	Pop observations	Rib variants				
			Bilateral 14th rib, left normal, right reduced	Unilateral left 14th rib reduced	Bilateral 14th ribs both reduced	Unilateral right 14th rib reduced	Bilateral 14th ribs, left reduced, right normal
49	13	N.A.D.					
50	13	N.A.D.					
51	11	N.A.D.					
52	5	N.A.D.		1			
53	9	N.A.D.		1			
54	10	N.A.D.		2			
55	9	N.A.D.	1				
57	13	N.A.D.					
58	8	N.A.D.					
59	8	N.A.D.		2	2	1	
60	14	N.A.D.		1			
61	10	N.A.D.					
63	12	N.A.D.					
64	8	N.A.D.		1			
66	10	N.A.D.					
67	9	N.A.D.					
69	12	N.A.D.					
70	12	No. 4. Tail much reduced, bitten off during weaning			4		2
71	13	N.A.D.					
72	10	N.A.D.			1		
73	11	N.A.D.		2			

N.A.D. = Nothing abnormal detected

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Table 23.2 Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat
Ioxynil technical 35 mg/kg : Weaning observations : Terminal necropsy and incidence of supernumerary 14th ribs

Dam No.	No. of pups in litter at weaning	Pup observations	Rib variants							
			Bilateral 14th rib, left normal, right reduced	Unilateral 14th rib reduced	Bilateral 14th ribs both reduced	Unilateral 14th rib reduced	Bilateral 14th ribs, left reduced, right normal	Bilateral 14th ribs	Unilateral right 14th rib	
74	12	† No. 11. Fluid filled mass adhering to tissue around spleen	2	1	5					
75	12	No. 9. Right anophthalmia, orbit reduced.		2	3		1			
76	11	No. 11. Right anophthalmia, orbit reduced.		3	3					
77	10	N.A.D.			4					
78	14	N.A.D.			10		1	2		1
79	8	N.A.D.			4			1		
80	8	N.A.D.	1				1			
81	11	N.A.D.		4			1			
82	11	N.A.D.			1		2			
83	13	N.A.D.		3			1			
84	10	No. 1. Increased renal pelvic cavitation (right)								
85	11	No. 4. Increased renal pelvic cavitation (right)		1	4		2			
86	10	N.A.D.		2	6					
87	9	N.A.D.		1						
91	5	N.A.D.								
92	11	N.A.D.			2		1			
94	10	N.A.D.		2	3					
95	10	N.A.D.		1	2					
98	11	N.A.D.		6	1		2			

† Histopathology performed
N.A.D. = Nothing abnormal detected

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Table 24

Toxynil technical : Teratogenicity study with littering phase,
by the oral route, in the rat

Foetal and weanling observations.

Incidence of hydroureter and supernumerary 14th ribs

Phase of study	Teratology		Littering	
	Control	35	Control	35
Number of pups examined	210	153	220	197
Bilateral hydroureter	1	*** 24	-	-
% bilateral hydroureter	0.5	14.3	-	-
Bilateral 14th rib, ossification normal	0	2	0	2
% bilateral 14th rib, ossification normal	0	1.2	0	1.0
Bilateral 14th rib, ossification reduced	8	*** 42	7	*** 48
% bilateral 14th rib, ossification reduced	3.8	25.0	3.2	24.4
Unilateral left 14th rib, ossification normal	0	1	0	0
% unilateral left 14th rib, ossification normal	0	0.6	0	0
Unilateral left 14th rib, ossification reduced	11	* 19	10	** 25
% unilateral left 14th rib, ossification reduced	5.2	11.3	4.5	12.7
Unilateral right 14th rib, ossification normal	0	0	0	1
% unilateral right 14th rib, ossification normal	0	0	0	0.5
Unilateral right 14th rib, ossification reduced	2	6	5	* 13
% unilateral right 14th rib, ossification reduced	1.0	3.6	2.3	6.6
Bilateral 14th rib, left ossification reduced, right normal ossification	0	1	1	3
% bilateral 14th rib, left ossification reduced, right normal ossification	0	0.6	0.5	1.5
Bilateral 14th rib, right ossification reduced, left normal ossification	0	* 4	1	3
% bilateral 14th rib, right ossification reduced, left normal ossification	0	2.4	0.5	1.5
Total supernumerary 14th ribs	21	*** 75	24	*** 95
% total supernumerary 14th ribs	10.0	44.6	10.9	43.2

Statistical analysis performed on a per litter basis

* p<0.05

** p<0.01

*** p<0.001

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Table 25

Ioxynil technical : Teratogenicity study with littering phase,
by the oral route, in the rat

Summary of Tables 23 and 24 (combining teratology and
littering phase data)

	Control	Ioxynil technical 35 mg/kg
Total number of pups	430	365
Bilateral 14th ribs, ossification normal	0	4
% bilateral 14th ribs, ossification normal	0	1.1
Bilateral 14th ribs, ossification reduced	15	*** 90
% bilateral 14th ribs, ossification reduced	3.5	24.7
Unilateral left 14th rib, ossification normal	0	1
% unilateral left 14th rib, ossification normal	0	0.3
Unilateral left 14th rib, ossification reduced	21	** 44
% unilateral left 14th rib, ossification reduced	4.9	12.1
Unilateral right 14th rib, ossification normal	0	1
% unilateral right 14th rib, ossification normal	0	0.3
Unilateral right 14th rib, ossification reduced	7	** 19
% unilateral right 14th rib, ossification reduced	1.6	5.2
Bilateral 14th ribs, left ossification reduced, right ossification normal	1	4
% bilateral 14th ribs, left ossification reduced, right ossification normal	0.2	1.1
Bilateral 14th ribs, right ossification reduced, left ossification normal	1	* 7
% bilateral 14th ribs, right ossification reduced, left ossification normal	0.2	1.9
Total supernumerary ribs	45	*** 170
% supernumerary ribs	10.5	46.6

* p<0.05

** p<0.01

*** p<0.001

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Table 26
Ioxynil technical : Teratogenicity study with littering phase,
by the oral route, in the rat

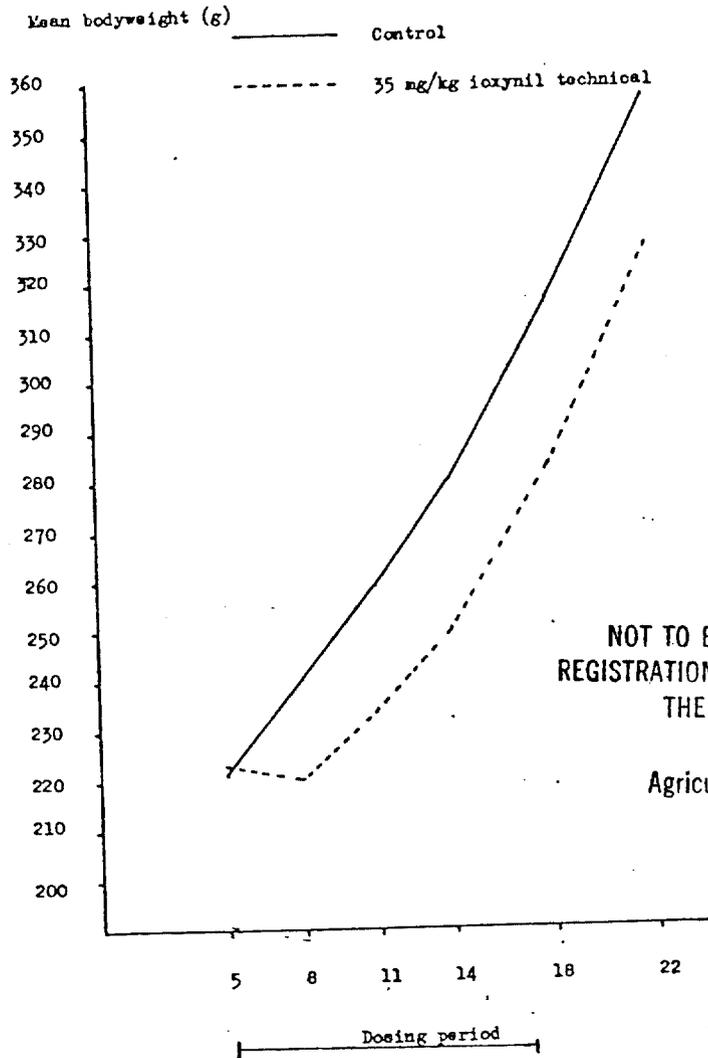
Littering phase histopathology

Dam number	Pup number	Sex	Dose group mg/kg	Macroscopic observations	Histopathological findings
90		♀	35	Female failed to litter. Necropsy revealed animal to be not pregnant. A blood filled mass adjacent to rectum/uterus.	Recent haematoma apparently arising in subserosal blood vessels of the rectal wall. Cause unknown.
74	11	♀	35	Fluid filled mass adhering to tissue around spleen.	Simple cystic structure lined by flattened epithelium or simple columnar epithelium, resembles a paraovarian cyst.

Fig 1

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat

Group mean bodyweights of teratology phase dams with viable young



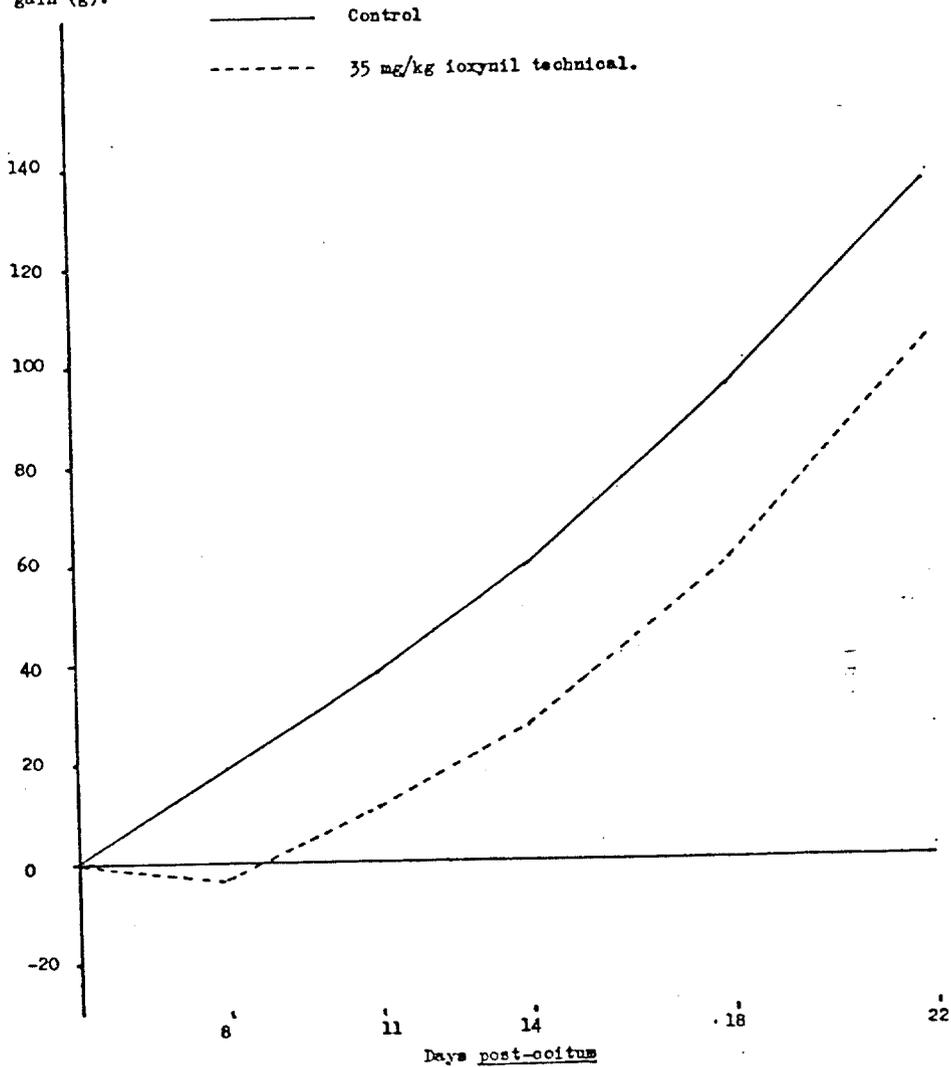
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Fig 2

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat

Group mean bodyweight gain days 5 to 22 post-coitum of teratology phase dams with viable young

Mean bodyweight gain (g).

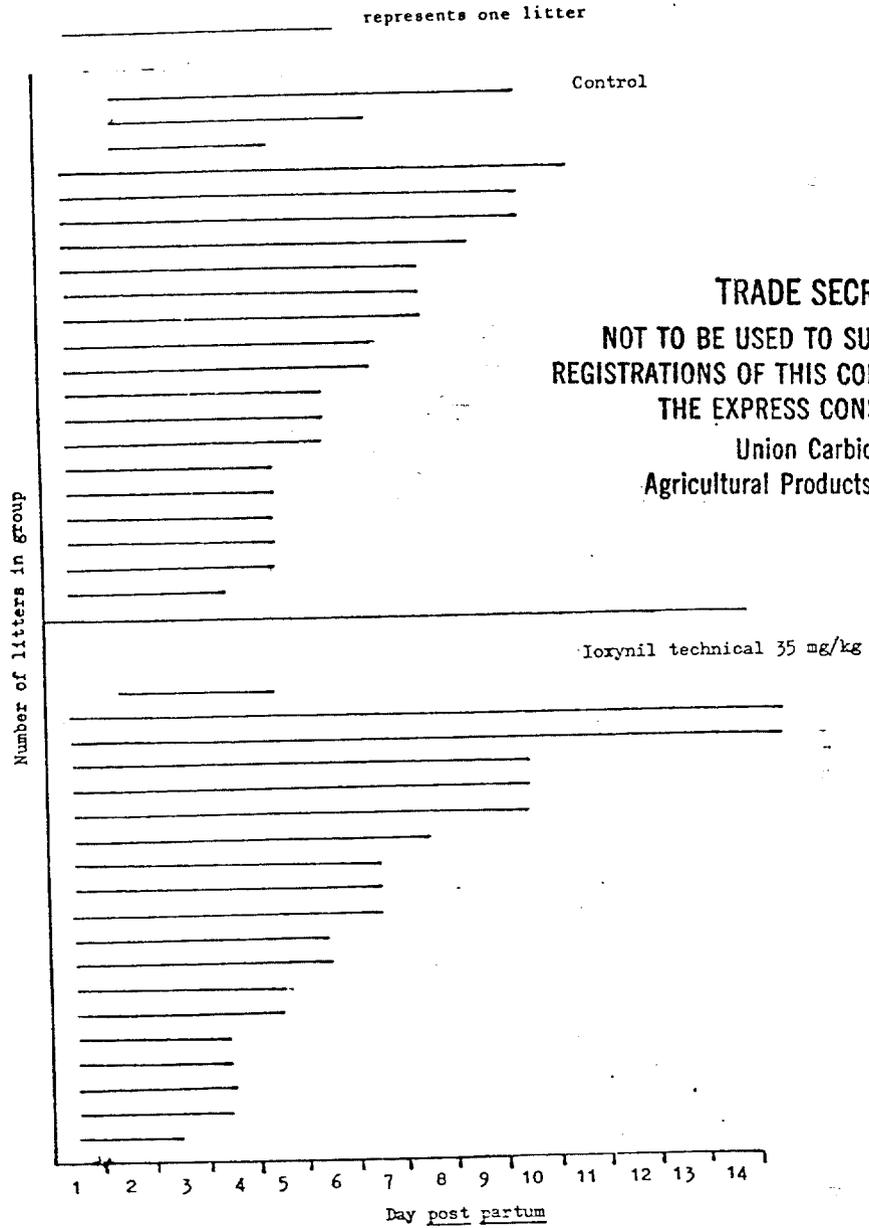


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Fig 3.1

Ioxynil technical : Teratogenicity study with littering phase,
by the oral route, in the rat.

Pup development - surface righting reflex



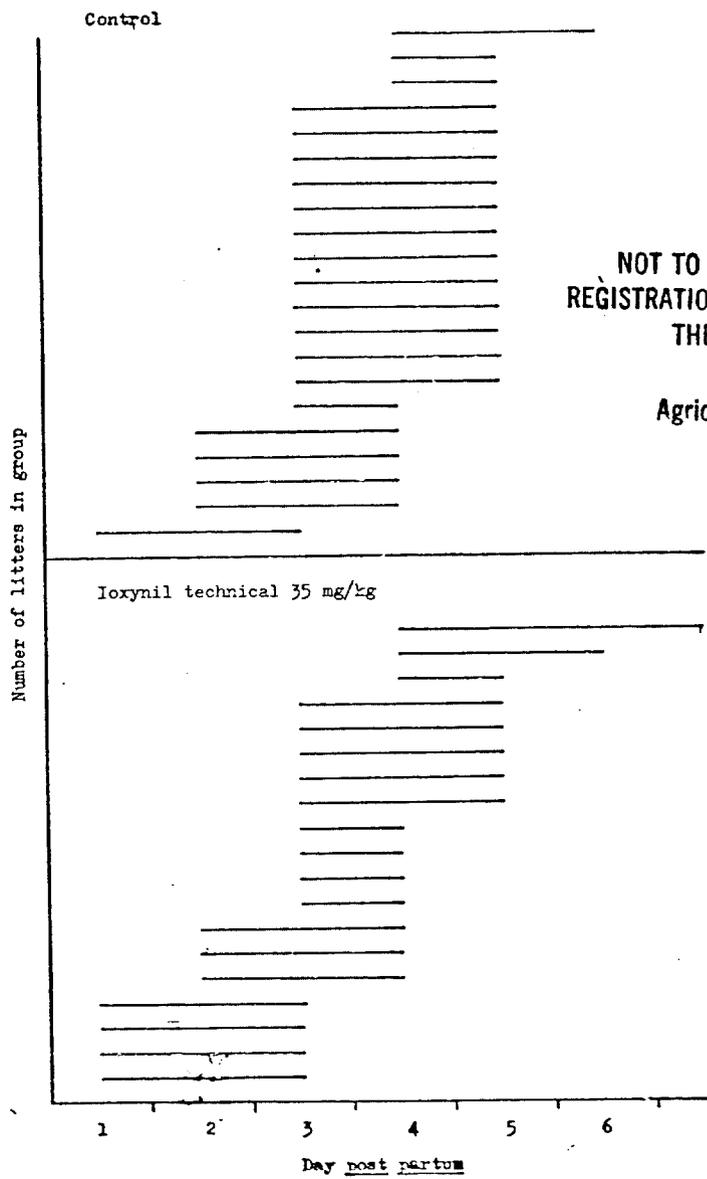
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Fig 3.2

Ioxynil technical : Teratogenicity study with littering phase,
by the oral route, in the rat

Pup development - pinna unfolding

_____ represents one litter

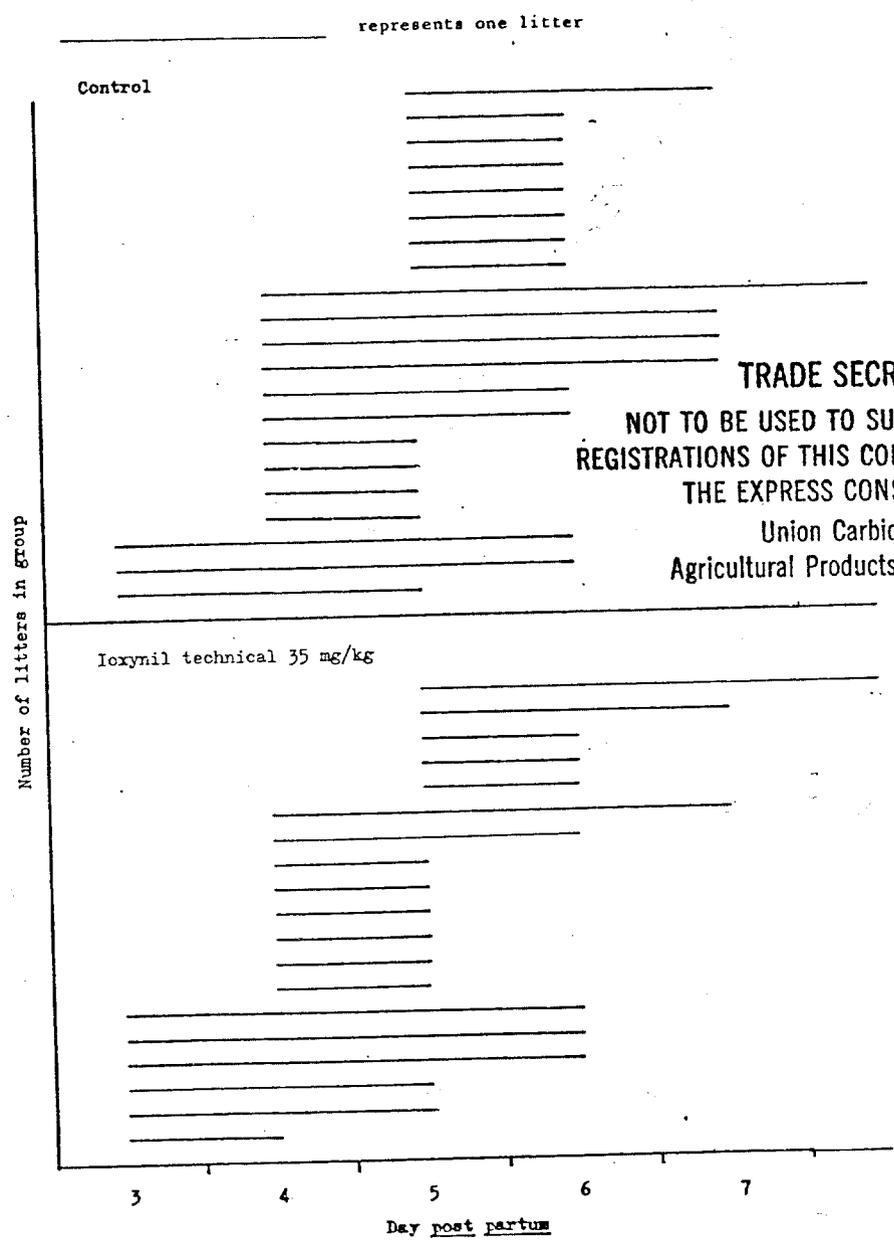


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Fig 3.3

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat

Pup development - hair growth (1st coat)

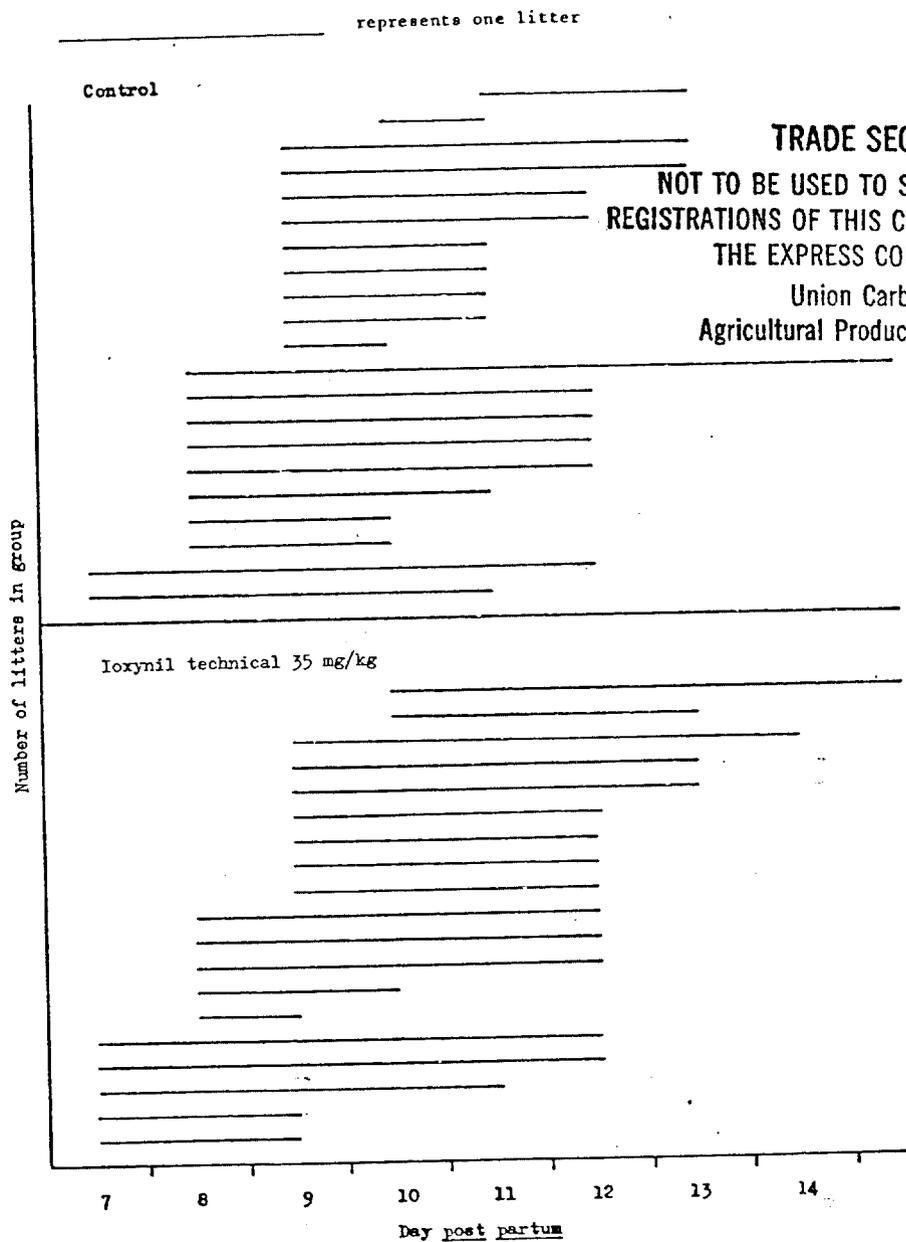


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Fig 3.4

Ioxynil technical : Teratogenicity study with littering phase,
by the oral route, in the rat

Pup development - eruption of upper incisors



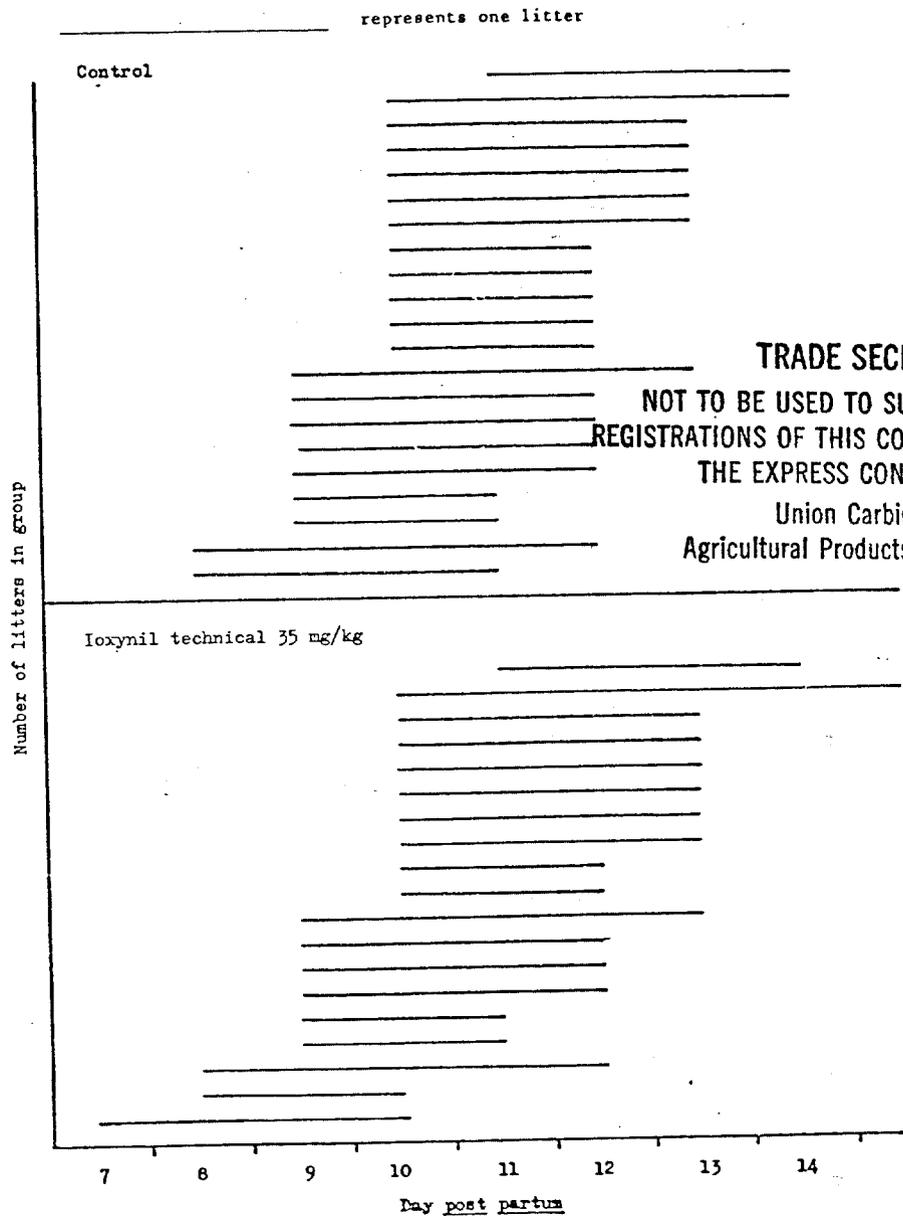
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Fig 3.5

Ioxynil technical : Teratogenicity study with littering phase,
by the oral route, in the rat

Pup development - eruption of lower incisors



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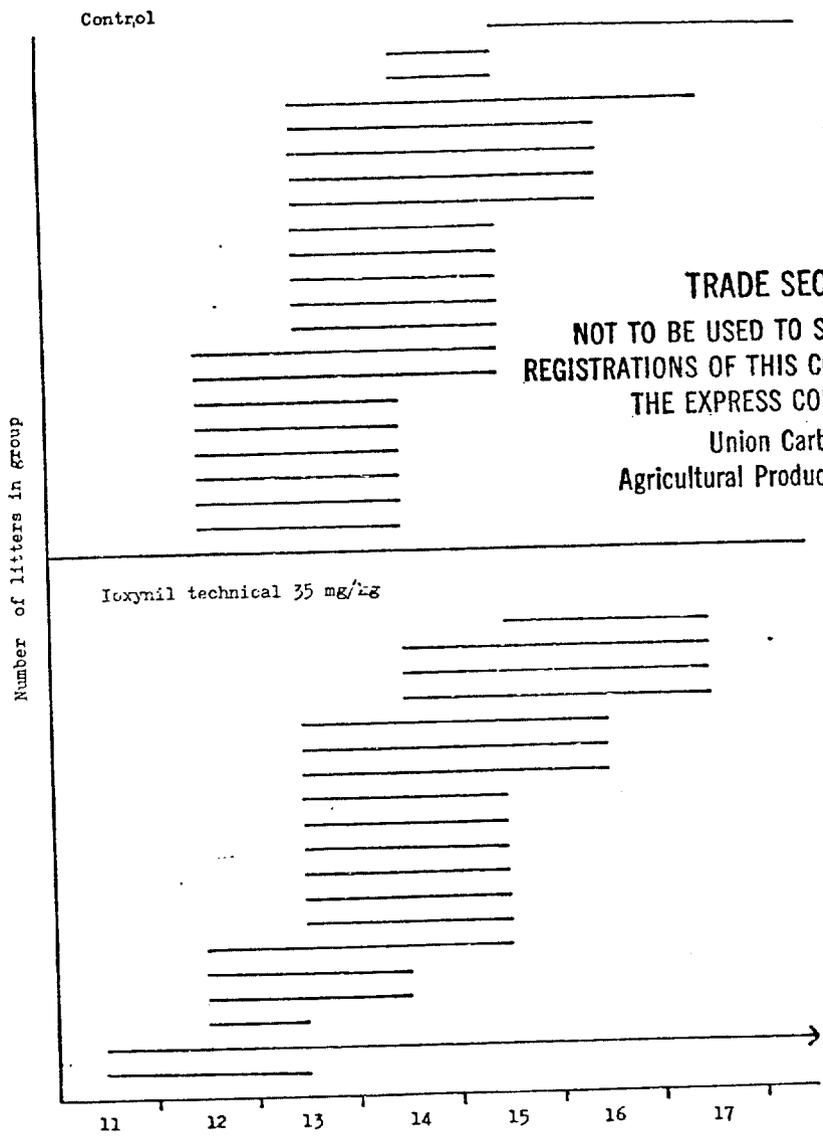
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Fig 3.6

Ioxynil technical : Teratogenicity study with littering phase,
by the oral route, in the rat

Pup development - startle response

_____ represents one litter



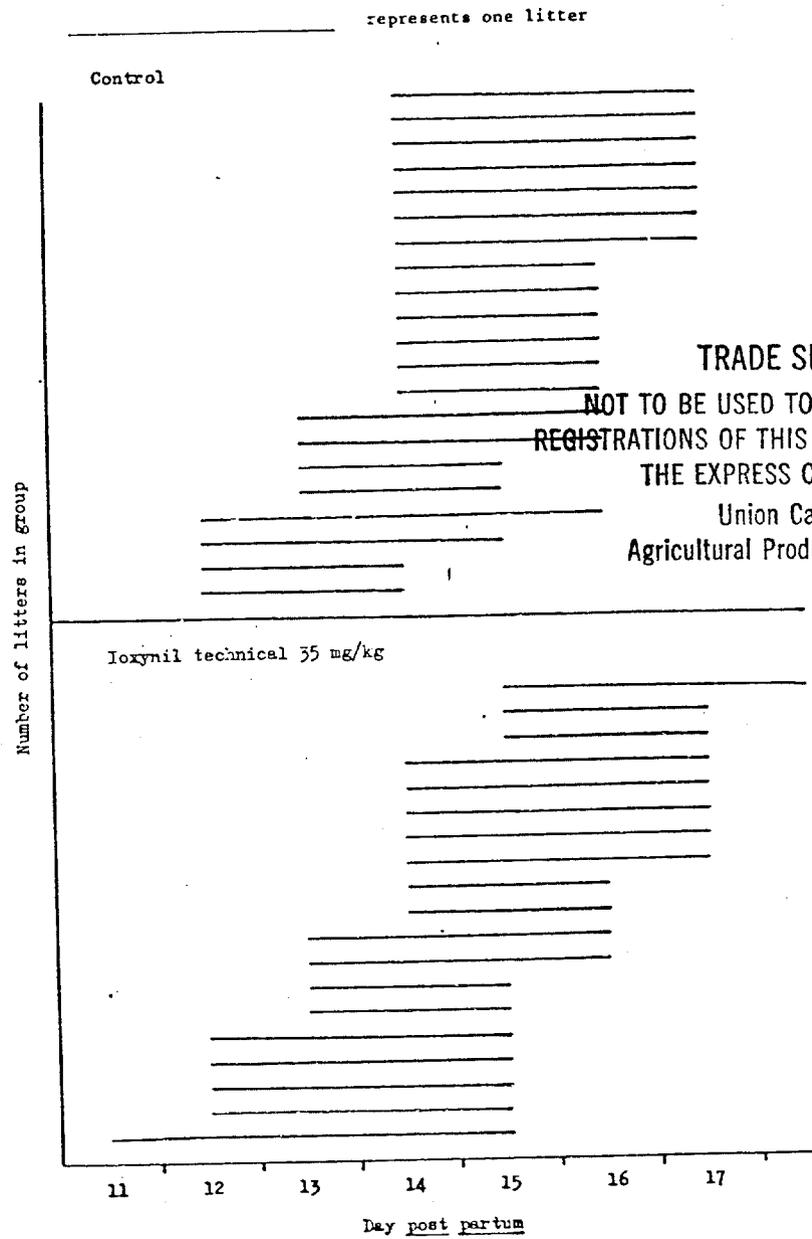
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† One pup (litter 94) did not give a full startle response throughout the testing period

Fig 3.7

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat

Pup development - eye opening



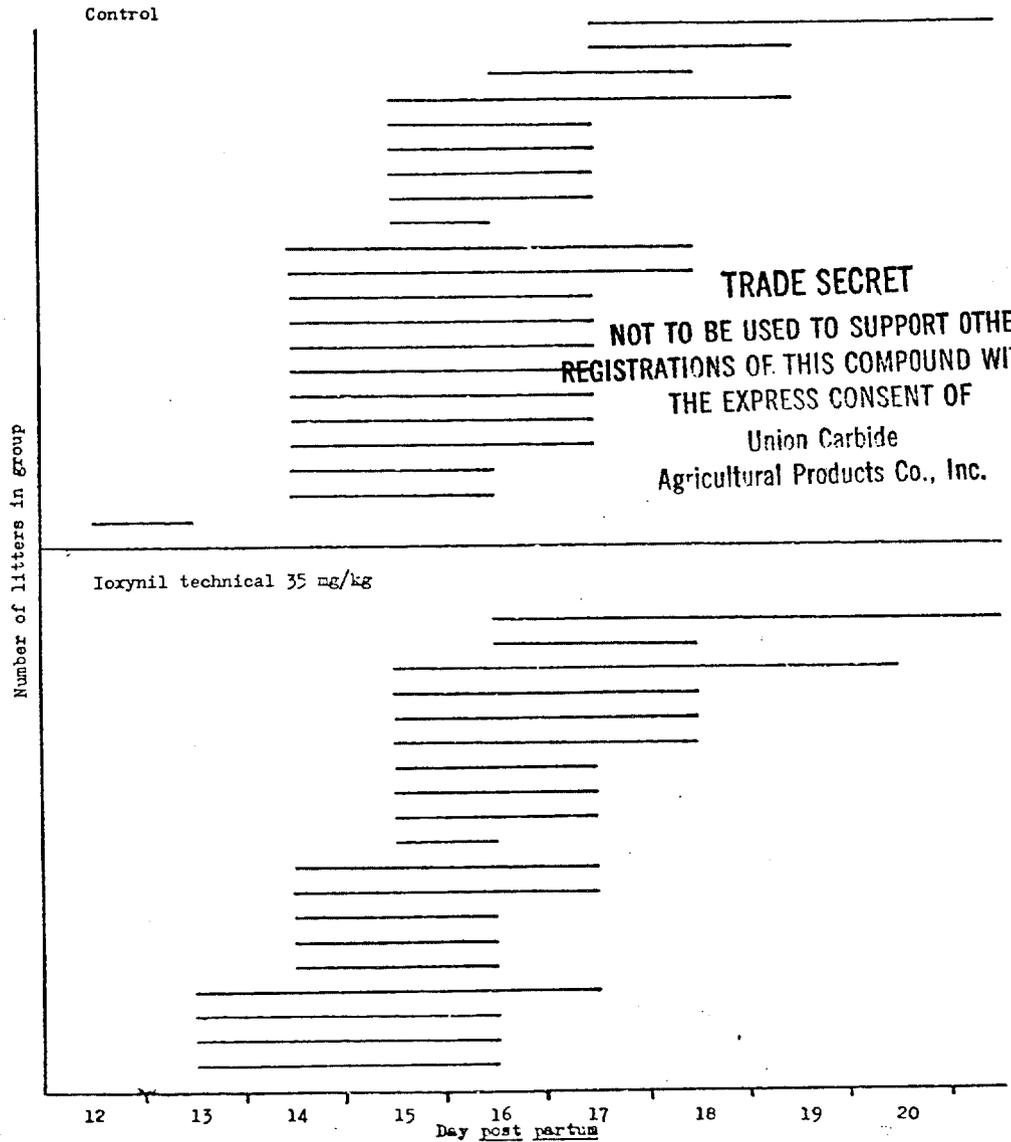
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Fig 3.8

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat

Pup development - hair growth (2nd coat)

_____ represents one litter

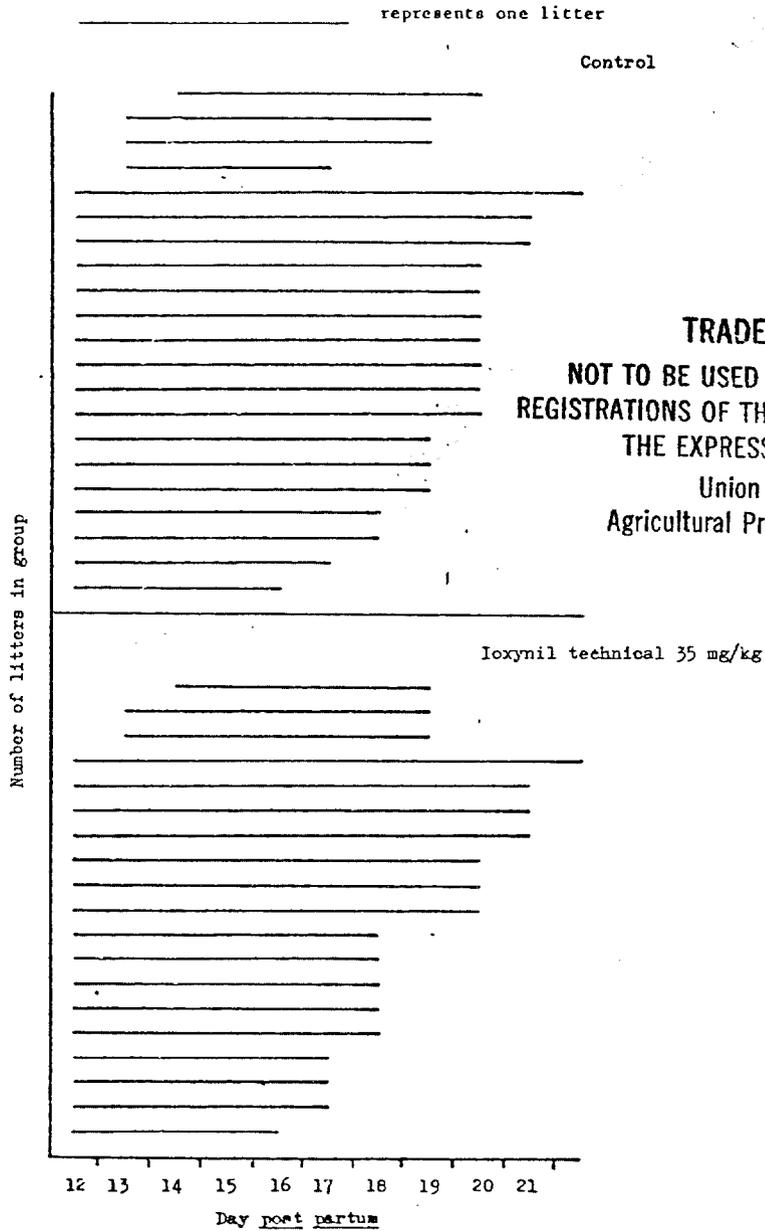


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Fig 3.9

Ioxynil technical : Teratogenicity study with littering phase,
by the oral route, in the rat

Pup development - air righting reflex



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GP

R.Tox.89

Signature:

G.P. Copping

Name:

G.P. Copping

Qualification:

H.N.D.

Appointment:

Reproductive Toxicology Unit Head

Work carried out at:

May & Baker Ltd., Dagenham, Essex

Date:

16th October 1981

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Union Carbide
Agricultural Products Co., Inc.

Signature:

M. Parry James

Name:

Michael Parry James

Qualification:

B.V.Sc., Ph.D., M.R.C.V.S.

Appointment:

Lecturer in Veterinary Pathology

Work carried out at:

Comparative Pathology Laboratory,
University of Bristol

Date:

27th October, 1981

BJ

QUALITY ASSURANCE COMPLIANCE

Ioxynil technical : Teratogenicity study with littering phase,
by the oral route, in the rat

The study reported here was inspected on the following dates:

26 and 27 February 1981

4, 6, 12, 19, 20 and 30 March 1981

6, 8, 14 and 24 April 1981

12 May 1981

The findings of these inspections were reported to the Line Managers
on 30 March 1981 and 9 June 1981.

The report was audited by the Quality Assurance Unit, being completed
on 16 October 1981, and has been found to describe accurately the methods
and S.O.P.'s used. The results also accurately reflect the raw data
from the study.

D.L. Colinese
Quality Assurance Unit

Dated : 16 October 1981

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APPENDIX I

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat



May & Baker Ltd
Pharmaceutical and Chemical Manufacturers

Sweet Briar Road
Norwich NR5 5AP
Telegrams: B.smith Norwich
Telex: Norwich 97152
Telephone: (0503) 47373

Our ref: CJB/WG Your ref: Date: 7.1.61.

ANALYTICAL REPORT

IOXYNIL TECHNICAL (DAMP)

Sample: H.1302 Batch No.: LW 1024

Appearance A very slightly brownish-cream powder.

Odour Slight.

Solution a) A solution of 5 g. in a mixture of 20 ml. N. sodium hydroxide and 30 ml. water is complete and almost bright.
b) A 5% solution of the dried material in acetone is complete.

Melting Point 209°C determined on the dried material.

Inorganic Halides 0.03% as Cl.

Sulphated Ash 0.1%.

Loss on Drying 10.6% at 105°C.

Related Impurities 1.5% w/w total, with reference to the dried material.

Assay a) Based on Iodine : 100.1% calculated with reference to the dried material.
b) By G.C. : 99.1% calculated with reference to the dried material.

Mineral Acid Content Negligible.

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Signed 
C.J. Basshan, C.Chem., M.R.S.C.,
Analytical Control, Norwich.



INITIALS 	REPORT REF. R.Tox.89	PAGE 78 OF 82
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APPENDIX II

Ioxynil technical : Teratogenicity study with littering phase,
by the oral route, in the rat

Dr. BERNARD DYER and PARTNERS (1948) Ltd.

DIRECTORS
Dr. J. H. HAMENCE, O.B.E., M.B.A., F.R.C.
P. B. HALL, M.Chem., F.R.G.
J. A. POTTER, M.Chem., F.R.G.

TELEPHONE—01-829 3254.
TELEGRAPHIC ADDRESS—BERNDYER, LONDON, E.C.3.
CABLEGRAMS—BERNDYER, LONDON.
TELEX—LONDON 28504/MONO REF. 2932.

Analytical Laboratory,

PEEK HOUSE,
20, EASTCHEAP.

LONDON, EC3M 1EL 2nd February, 1981

Result of Analysis 129

Of a Sample of Sawdust

Sent on Account of Sawdust Marketing Co.

Received on 8th January, 1981

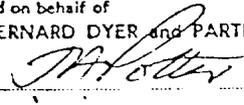
Marked Marked DO

Sealed UNSEALED

Dioldrin less than 0.31 parts per million

Pentachlorophenol less than 0.5 parts per million

For and on behalf of
Dr. BERNARD DYER and PARTNERS (1948) Ltd.



Form A9 5

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APPENDIX III

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat



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THE CHRISTOPHER HILL GROUP LIMITED
 P.O. BOX 6, AGRARIAN HOUSE, CASTLE STREET, POOLE, DORSET, BH15 1HL (REGISTERED OFFICE)
 TELEPHONE: POOLE (02013) 70561. TELEX: 41135

EXTENDED ANALYSIS SERVICE
 ASSAYED AT THE LORD RANK RESEARCH CENTRE, HIGH WYCOMBE

NAME May & Baker Limited

CERTIFICATE OF ANALYSIS - DIETS

Production Details		Reporting of Results	
Batch No:	SVD 105	Certificate Number	LEAD/ 307
Product:	CR4X	Date Reported	13th December, 1980
Date of Manufacture:	2nd December, 1980	Analyst Reporting	Miss M. Bacon

RESULTS BY ANALYSIS

CONTAMINANTS

Total Viable Count (30°C)	3.0x10 ³	cfu/g
Mesophilic Spores	100	cfu/g
Salmonella in 50g	Absent	
Coliforms	Less than 3	MPN/g
Faecal Coliforms	Less than 3	MPN/g

Arsenic	0.26	mg/kg	Total DDT	Less than 0.02	mg/kg
Cadmium	0.06	mg/kg	Dieldrin	Less than 0.01	mg/kg
Lead	0.3	mg/kg	Lindane	Less than 0.01	mg/kg
Mercury	0.01	mg/kg	Heptachlor	Less than 0.01	mg/kg
Selenium	0.18	mg/kg	Malathion	Less than 0.05	mg/kg
Nitrate	2	mg/kg	Total P.C.S's	Less than 0.1	mg/kg
Nitrite	0.5	mg/kg	Total Aflatoxins	Less than 5	ppb

Signed Margaret Bacon

Analyst Reporting

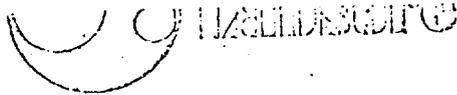
Checked by JB

Head of Laboratory

INITIALS <i>[Signature]</i>	REPORT REF. R.Tox.89	PAGE 00 OF 82
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APPENDIX III (continued)

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat



THE CHRISTOPHER HILL GROUP LIMITED
P.O. BOX 6, AGRARIAN HOUSE, CASTLE STREET, POOLE, DORSET, BH15 1HL (REGISTERED OFFICE)
TELEPHONE: POOLE (07073) 70561, TELEX: 41135

EXTENDED ANALYSIS SERVICE
ASSAYED AT THE LORD BANK RESEARCH CENTRE, HIGH WYCOMBE

NAME May & Baker Limited

CERTIFICATE OF ANALYSIS - DIETS

Production Details		Reporting of Results	
Batch No:	SU2 109	Certificate Number	LEA/01 307
Product:	CRMX	Date Reported	18th December, 1980
Date of Manufacture:	2nd December, 1980	Analyst Reporting	Miss M. Bacon

RESULTS BY ANALYSIS

NUTRIENTS		
Moisture	9.9	%
Crude Oil	1.5	%
Crude Protein	18.8	%
Crude Fibre	2.1	%
Ash	4.9	%
Phosphorus	0.66	%
Chloride	0.51	%
Calcium	0.77	%
Magnesium	0.18	%
Sodium	0.26	%
Potassium	0.72	%
Zinc	39	mg/kg
Manganese	60	mg/kg
Copper	13	mg/kg
Iron	140	mg/kg
Vitamin A	6,480	iu/kg
Vitamin C (where added)		mg/kg
Vitamin E	53	iu/kg

TRADE SECRET
NOT TO BE USED TO SUPPORT OTHER
REGISTRATIONS OF THIS COMPOUND WITHOUT
THE EXPRESS CONSENT OF
Union Carbide
Agricultural Products Co., Inc.

Signed Margaret Bacon Analyst Reporting
Checked By [Signature] Head Of Scientific Services

NOT TO BE USED TO SUPPORT OTHER REGISTRATIONS OF THIS COMPOUND WITHOUT THE EXPRESS CONSENT OF

Union Carbide Agricultural Products Co., Inc.

APPENDIX IV

Ioxynil technical : Teratogenicity study with littering phase, by the oral route, in the rat

Dr. BERNARD DYER and PARTNERS (1948) Ltd.

DIRECTORS:
 DR. J. N. HAMENCE, O.B.E., M.Chem., F.R.S.C.
 P. S. HALL, M.Chem., F.R.S.C.
 J. A. POTTER, M.Chem., F.R.S.C.

TELEPHONE—01-826 9234
 TELEGRAPHIC ADDRESS—BERNDYER, LONDON, E.C.3.
 CABLEGRAMS—HEMNDYER, LONDON.
 TELEX—LONDON 28802/MONO REF 2932.

Analytical Laboratory,

PEEK HOUSE,
 20, EASTCHEAP,

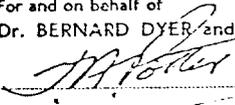
LONDON, EC3M 1EL 12th March 1981

Result of Analysis 480

Of a Sample of Water
 Sent on Account of May and Baker Ltd.
 Received on 26th January 1981
 Marked From K5 and L4 Toxicology Unit D47 Building Expt Nos
81/004 81/003 and 80/156 06.01.81
 Sealed Unsealed

						PARTS PER MILLION
Lead	less than 0.01
Copper	less than 0.01
Zinc	0.24
Cadmium	less than 0.01
Mercury	less than 0.01
Arsenic	less than 0.01
Selenium	less than 0.001
Aflatoxin B1	less than 0.0001
B2 G1 & G2	less than 0.0001
Total DDT (DDE, DDT, TDE)	less than 0.001
Dieldrin	less than 0.001
Lindane	less than 0.001
Heptachlor	less than 0.001
Malathion	less than 0.001
Polychlorinated Biphenyls	less than 0.001

For and on behalf of
 Dr. BERNARD DYER and PARTNERS (1948) Ltd.



TRADE SECRET
 NOT TO BE USED TO SUPPORT OTHER
 REGISTRATIONS OF THIS COMPOUND WITHOUT
 THE EXPRESS CONSENT OF
 Union Carbide
 Agricultural Products Co., Inc.

Appendix V

Ioxynil technical : Teratogenicity study with littering phase,
by the oral route in the rat

Analysis^o by high-performance liquid chromatography of dosage forms

Dosage form Nominal % w/v ioxynil technical	Found % w/v ioxynil					Mean Found % Nominal
	Date of preparation [†]					
	13.02.81	20.02.81	27.02.81	06.03.81	13.03.81	Uncorrected # Corrected
0.7	0.557	0.611	0.606	- 0.590	0.600	85.10 96.64
	0.566	0.615	0.606	0.579	0.601	
	0.583	0.597	0.601	0.601	0.610	
	0.589	0.586	0.601	0.597	0.612	
	0.578	0.602	0.605	0.632	0.582	
	0.575	0.608	0.607	0.602	0.573	

^o Triplicate samples analysed in duplicate. Values presented are uncorrected for impurity and water content.

[†] Date of analysis for all samples : 25.03.81

[#] For impurity and water content (11.94% total)

R.4.3



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

Glenn S. Simon, Ph.D., DABT
Director of Toxicology
Rhône-Poulenc
P.O. Box 12014
2 T.W. Alexander Drive
Research Triangle Park, North Carolina 27709

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

APR 06 1995

EPA acknowledges the receipt of information submitted by your organization under Section 8(e) of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA §8(e) Document Control Number (e.g., 8EHQ-00-0000) assigned by EPA to your submission(s). Please cite the assigned 8(e) number when submitting follow-up or supplemental information and refer to the reverse side of this page for "EPA Information Requests".

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Please address any further correspondence with the Agency related to this TSCA 8(e) submission to:

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Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Washington, D.C. 20460-0001

EPA looks forward to continued cooperation with your organization in its ongoing efforts to evaluate and manage potential risks posed by chemicals to health and the environment.

Sincerely,

Terry R. O'Bryan
Terry R. O'Bryan
Risk Analysis Branch

Enclosure

12593A



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Triage of 8(e) Submissions

Date sent to triage: 12/8/95

NON-CAP

CAP

Submission number: 12593A

TSCA Inventory:

Y N D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX SBTOX SEN w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

STOX CTOX EPI RTOX GTOX
STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

Other (FATE, EXPO, MET, etc.): _____

Notes:

THIS IS THE ORIGINAL 8(e) SUBMISSION; PLEASE REFILE AFTER TRIAGE DATABASE ENTRY

For Contractor Use Only

entire document: 0

1

2

pages 1, 2

pages 1, 2, 16

Notes:

Contractor reviewer: FDK

Date: 3/13/95

CECATS TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA: Submission # 8EHO 1092-1253 SEQ. A
 TYPE INT. SUPP FLWP
 SUBMITTER NAME: Rhone-Poulenc Inc.

INFORMATION REQUESTED: FLWP DATE: _____
 0501 NO INFO REQUESTED
 0502 INFO REQUESTED (TECH)
 0503 INFO REQUESTED (VOL ACTIONS)
 0504 INFO REQUESTED (REPORTING RATIONALE)
 DISPOSITION:
 0509 REFER TO CHEMICAL SCREENING
 0578 CAP NOTICE

SUB. DATE: 09/14/92 OTS DATE: 10/07/92 CSRAD DATE: 02/09/95
 CHEMICAL NAME: Bronzofenil, 4 hydroxy-3,5-diodo-1 oxynil
 CAS# 1689-83-4
11

OPTIONARY ACTIONS:
 0401 NO ACTION REPORTED
 0402 STUDIES PLANNED (INSTRUMENTAL)
 0403 NOTIFICATION OF WORKER CONCERNS
 0404 LABELING CHANGES
 0405 PROCESS/HANDLING CHANGES
 0406 APP/USE DISCONTINUED
 0407 PRODUCTION DISCONTINUED
 0408 CONFIDENTIAL

INFORMATION TYPE:	P F C	INFORMATION TYPE:	P F C	INFORMATION TYPE:	P F C
0201 ONCO (HUMAN)	01 02 04	EPICLIN	01 02 04	0241 IMMUNO (ANIMAL)	01 02 04
0202 ONCO (ANIMAL)	01 02 04	HUMAN EXPOS (PROD CONTAM)	01 02 04	0242 IMMUNO (HUMAN)	01 02 04
0203 CELL TRANS (IN VITRO)	01 02 04	HUMAN EXPOS (ACCIDENTAL)	01 02 04	0243 CHEMOPHYS PROP	01 02 04
0204 MUTA (IN VITRO)	01 02 04	HUMAN EXPOS (MONITORING)	01 02 04	0244 CLASTO (IN VITRO)	01 02 04
0205 MUTA (IN VIVO)	01 02 04	ECO/AQUA TOX	01 02 04	0245 CLASTO (ANIMAL)	01 02 04
0206 REPRO/TERATO (HUMAN)	01 02 04	ENV. OCCUREL/FATE	01 02 04	0246 CLASTO (HUMAN)	01 02 04
0207 REPRO/TERATO (ANIMAL)	01 02 04	EMER INCI OF ENV CONTAM	01 02 04	0247 DNA DAM/REPAIR	01 02 04
0208 NEURO (HUMAN)	01 02 04	RESPONSE REQUEST DELAY	01 02 04	0248 PROD/USE/PROC	01 02 04
0209 NEURO (ANIMAL)	01 02 04	PROD/COMP/CHEM ID	01 02 04	MSDS	01 02 04
0210 ACUTE TOX. (HUMAN)	01 02 04	REPORTING RATIONALE	01 02 04	OTHER	01 02 04
0211 CHR. TOX. (HUMAN)	01 02 04	CONFIDENTIAL	01 02 04		
0212 ACUTE TOX. (ANIMAL)	01 02 04	ALLERG (HUMAN)	01 02 04		
0213 SUB ACUTE TOX (ANIMAL)	01 02 04	ALLERG (ANIMAL)	01 02 04		
0214 SUB CHRONIC TOX (ANIMAL)	01 02 04	METAB/PHARMACO (ANIMAL)	01 02 04		
0215 CHRONIC TOX (ANIMAL)	01 02 04	METAB/PHARMACO (HUMAN)	01 02 04		

TRIAJE DATA: NON-CBI INVENTORY YES NO (CONTINUE) REFER

USE: R: D Pesticide Import
 PRODUCTION:

TOXICOLOGICAL CONCERN: LOW MED HIGH

SPECIES: RAT

ONGOING REVIEW: YES (DROP/REFER) NO (CONTINUE) REFER

IN IT (ANIMAL)

35 mg/kg - refer to toxicology in body not gains in some fetal wt. significant increase of incidence of increased, increased incidence of supernumerary ribs.

Develop a offspring checked today & 1 wk. only one done