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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 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 the observation of statistically significant increases in hydroureter and supernumerary ribs. Rats were dosed by gavage on gestation days 5 through 17 with either 0, 5, 15, or 35 mg/kg/day (28 females/group). Treatment with ioxynil at 35 mg/kg/day caused maternal toxicity consisting of six deaths, impairment of body weight gains from the onset of dosing through to termination, and a reduction in food consumption during gestation days 5 to 8. A very slight reduction in maternal body weight gain was also seen at 15 mg/kg/day. Mean fetal weight was significantly reduced and the incidences of minor anomalies and hydroureter were statistically increased at 35 mg/kg/day. A dose-related increase in the incidence of supernumerary 14th ribs was also observed.

mm 10/6/92

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

IOX-TP-81-1903

120

M&B May & Baker

Pharmaceutical and Chemical Manufacturers. Dagenham, Essex, RM10 7XS England.

Classification

Origin

Report Ref. R.Tox.12

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Date February 1981

Pages 1 - 69

Computer Reference

CONFIDENTIAL

IOXYNIL TECHNICAL

Teratogenicity Study by the Oral Route in the Rat

Scientific report from the Research Laboratories

of

May & Baker Ltd.

by

G.P. Copping H.N.D.

UNION CARBIDE EUROPE S.A.
Rue Pedro Meylan 5
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SUMMARY

In this assessment of the effect of ioxynil technical on pregnancy of the rat, animals were dosed once on each of days 5 to 17 post-coitum with either 0, 5, 15 or 35 mg/kg ioxynil.

Treatment with ioxynil at 35 mg/kg was associated with six deaths and impairment of bodyweight gain from the onset of dosing through to termination. A reduction in food consumption during days 5 to 8 post-coitum was also associated with treatment at this dosage.

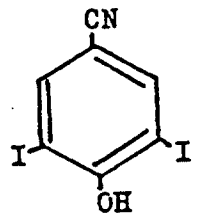
A very slight reduction in bodyweight gain was seen at 15 mg/kg ioxynil.

Litter parameters were essentially unaffected by treatment with ioxynil. However, the incidence of minor anomalies, especially hydroureter, was statistically significantly increased at 35 mg/kg ioxynil.

A dose related trend in the incidence of the supernumerary 14th rib variant was associated with treatment at all dosages of ioxynil tested.

1. MATERIALS

Ioxynil is 3,5-diiodo-4-hydroxybenzonitrile



Material from batch number KN 503 was used in this study.

Analytical data for the batch used are given in Analytical Report BJF/WG of 7th March 1979 (see Appendix I).

2. METHODS (Protocol Ref:STUDY/TA/80/160/01)

2.1 Animals

One hundred and twelve mated female CD strain rats received on 19th and 26th September 1980 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.

2.2 Animal accommodation

The rats were housed in fours in batteries of metal cages with grid floors, in room K5 of D47 building, May & Baker Research Institute. The room had forced air ventilation and a daily photoperiod of at least 14 hours (06.00 h to 20.00 h). The temperature of the room was not strictly controlled, but was in the region of 21°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 (Federal Register July 1979), and certificates of analysis were obtained (Appendix II).

2.4 Dosing

The rats were individually identified by an ear clipping system and randomly assigned to four treatment groups, each of 28 animals.

Rats were dosed orally once on each of days 5 - 17 post-coitum, by means of a metal oesophageal tube, with either 0, 5, 15 or 35 mg ioxynil per kilogram bodyweight in the form of aqueous suspensions containing 0.25% w/v gum tragacanth, prepared freshly each week.

Control rats received the vehicle only. The volume administered to each rat was 5 ml per kilogram bodyweight per day (0, 0.1, 0.3 or 0.7% w/v ioxynil). Dosages were adjusted according to the animal's bodyweight on the day of dosing.

2.5 Observations

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.

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.

The rats were killed on day 22 post-coitum by an intra-cardiac injection of sodium pentobarbitone solution, 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.

Individual viable foetuses were weighed, sexed and examined in detail for external abnormalities and by dissection, after an intra-thoracic injection of sodium pentobarbitone solution.

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).

2.6 Calculations

2.6.1 Pre-implantation loss was defined as

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

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

2.6.2 Post-implantation loss was defined as

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

2.6.3 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.

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

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

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

2.6.4 Food consumption calculations

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

2.7 Statistical analysis

Statistical evaluation of the results was by means of:

2.7.1 Students 't' test (food consumption, numbers of corpora lutea, numbers of implantations, numbers of viable foetuses and mean pup weight).

2.7.2 Mann-Whitney 'U' test (gestational bodyweights and bodyweight gain).

2.7.3 Chi squared test (pre-implantation loss, post-implantation loss, foetal sex ratio, numbers of foetal major malformations, minor anomalies and variants).

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

3. RESULTS

3.1 Parent animals

3.1.1 Clinical signs and mortalities (Table 1)

Six rats (numbers 87, 100, 103, 106, 109 and 112) from the 35 mg/kg ioxynil dosage group were found dead on days 10, 8, 8, 8, 9 and 7 post-coitum respectively. Cannibalism rendered post mortem examination impossible. There were no other mortalities or visible adverse reactions to treatment with ioxynil at any dose level tested.

3.2 Bodyweight (Tables 2 and 3, Figures I and II)

In comparison with the vehicle control animals the gestational bodyweights of dams with viable young in the 35 mg/kg ioxynil group were statistically significantly reduced ($p < 0.01$) throughout the dosing and post dosing periods.

The mean bodyweights of animals in the 15 mg/kg ioxynil group were statistically comparable with those of the vehicle control group, but showed a slight depression during both the dosing and postdosing periods. The bodyweights of animals in the 5 mg/kg ioxynil group were statistically comparable to those of the vehicle controls, group mean bodyweights being higher than those of the controls throughout the study.

3.3 Food consumption (Table 4 and 5)

Between days 5 and 8 of the dosing period, group mean food consumption (g/rat/day) of animals in the 35 mg/kg ioxynil dosage group was statistically significantly reduced ($p < 0.001$) when compared to that of the vehicle control group.

There were no other statistically significant differences in food consumption at 35 mg/kg ioxynil. There were no statistically significant differences in food consumption between animals dosed with 5 or 15 mg/kg ioxynil and the vehicle control group.

3.4 Pregnancy rates (Table 7)

The pregnancy rates in the various groups were very similar. However, pregnancy data were not available from the six animals in the 35 mg/kg ioxynil group which died, cannibalism preventing post-mortem examination.

3.5 Litter data (Tables 6 and 7)

Of the 16 animals stated by the supplier to have been found mated on the same day (23rd September, 1980) three were found to be non-pregnant and one animal died during the course of the study.

The remaining 12 were found to have litters with reduced foetal weights and reduced osteogenesis, indicative of an earlier than 22 day post-coitum foetus.

As all 12 animals were stated by the supplier to have mated on the same day and similar occurrences have happened before it seems reasonable to conclude that this was possibly a labelling error on the part of the breeder.

Foetal weight and skeletal data from these twelve litters Control (17,18,19 and 20), 5mg/kg ioxynil(45,46 and 47), 15mg/kg ioxynil (73,74,75 and 76), 35mg/kg ioxynil(101), were excluded from group analysis, except where indicated.

3.5.1 Implantations and pre-implantation loss

The mean number of implantations per litter was essentially comparable for all groups and inter-group differences were not statistically significant.

Pre-implantation losses were statistically comparable with the concurrent vehicle control group.

3.5.2 Litter size and post-implantation loss (Tables 6 and 7)

The mean numbers of viable foetuses per litter were comparable and intergroup differences were not statistically significant.

Post-implantation losses in animals treated with ioxynil were lower than those of the vehicle controls.

Intergroup differences were not statistically significant.

3.5.3 Mean foetal weight (Table 6 and 7)

A statistically significant ($p<0.001$) reduction in mean foetal weight was associated with treatment at 35mg/kg ioxynil. There were no other statistically significant differences in mean foetal weights at any other ioxynil treatment level when compared with the vehicle controls.

3.5.4 Major malformation and minor anomaly (Table 8, 9 and 10)

Neither the type nor the incidence of major malformation suggested any association with treatment with ioxynil at any dosage.

Intergroup differences were not statistically significant.

However, in comparison with the vehicle controls there was a statistically significant ($p < 0.01$) increase in the number of minor anomalies associated with treatment at 35 mg/kg ioxynil, this being mainly due to the increased incidence of hydroureter when compared to the vehicle control group.

The incidences of hydroureter in the other ioxynil treatment groups showed no increase over that observed for the concurrent vehicle controls.

There were no statistically significant differences in the numbers of other minor anomalies in any other ioxynil treatment group when compared to the vehicle controls.

A dose related increase in the incidence of the supernumerary 14th rib variant was associated with treatment with ioxynil.

Statistical evaluation on a litter basis revealed that the number of litters with foetuses exhibiting a 14th rib variant was statistically significantly increased, ($p < 0.001$) at 35 mg/kg ioxynil, and ($p < 0.01$) at 15 mg/kg ioxynil, when compared to the vehicle control animals. Although the number of litters with foetuses exhibiting a 14th rib variant was increased at 5 mg/kg ioxynil, this was not significant statistically when compared to the vehicle controls.

3.6 Diet and water analysis (Appendix II)

Analytical data on the batch of diet used in this study and a sample of tap water revealed no abnormal results for the contaminants tested. All results were within the limits (Federal Register 1979) quoted.

3.7 Analysis of dosage forms (Appendix III)

Analytical data from the three, weekly dosage form preparations revealed the overall mean percentage nominal ioxynil content to be within approximately $\pm$ 10% of that expected at 5mg/kg ioxynil, and

within approximately ± 1% at both 15 and 35 mg/kg ioxynil.

Individual results, however, from the second and third weekly samples revealed percentage nominal ioxynil levels to be increased by approximately 15% at 5 mg/kg ioxynil. This could not be explained in terms of sampling or dilution errors.

4. DISCUSSION

There were six deaths associated with treatment with ioxynil at 35 mg/kg, all the animals dying within the first 5 days of treatment.

The surviving animals in the 35 mg/kg ioxynil group showed a statistically significant ($p < 0.01$) reduction in bodyweight throughout the dosing and post-dosing periods. Treatment with 15 mg/kg ioxynil was associated with a reduction, although not statistically significant, in bodyweight over the same period as the 35 mg/kg ioxynil dosage group.

The above findings were consistent with those of a preliminary rangefinding study which revealed bodyweight reductions at 35 mg/kg/day and deaths at 40 mg/kg/day ioxynil.

It is therefore concluded that the deaths and bodyweight gain reductions in this study were directly related to treatment with ioxynil.

The only apparent effect of treatment with ioxynil on food consumption was a statistically significant reduction in group mean food intake at 35 mg/kg during the initial part of the dosing period. There were no other statistically significant differences in food consumption at any dosage of ioxynil when compared with the vehicle control group.

Litter parameters remained essentially unaffected by treatment with ioxynil. However, the statistically significant reduction in mean foetal weight observed in the 35 mg/kg dosage group may possibly be related to maternal toxicity, rather than a direct effect upon the foetus.

The incidence of hydroureter associated with treatment at 35 mg/kg ioxynil is within the range quoted in various background data available for this strain of rat. Nevertheless, in view of the statistically significant increase in the incidence of hydroureter at 35 mg/kg ioxynil, and the similarities in incidence between the vehicle control group and animals treated with 5 and 15 mg/kg ioxynil, it must be concluded that this increase in hydroureter at 35 mg/kg is compound related.

Various background data indicate that rats of this strain show a high incidence of supernumerary 14th rib variants, but the statistically significant dose related trend associated with ioxynil treatment cannot be explained purely in terms of a spontaneous effect. Although the number of animals showing 14th rib variants at 5 mg/kg ioxynil was not statistically significantly increased, the level was far higher than that

exhibited by the vehicle controls. The dose related effect upon the incidence of 14th rib variants can only be regarded as a compound related effect.

5. CONCLUSION

It is concluded that ioxynil technical administered to pregnant rats at 35 mg/kg was directly associated with six maternal deaths, a marked reduction in bodyweight during the dosing and post-dosing periods and a reduction in food consumption during the initial part of the dosing period. Reduction in mean foetal weight observed at 35 mg/kg ioxynil may have been caused by the maternal toxicity induced, rather than as a direct effect of treatment.

Minor foetal anomalies, particularly hydroureter, were statistically significantly affected by treatment with 35 mg/kg ioxynil only. The 14th rib variant was increased at all dosages of ioxynil tested.

Slight maternal toxicity was observed at 15 mg/kg ioxynil as exhibited by reductions in bodyweight. This must also be concluded as being compound related.

References

Dawson, A. B. (1926). Note on the staining of the skeleton of cleared skeletal specimens with Alizarin red S. Stain Techn., 1 : 123 - 4.

Federal Register/Vol. 44, No. 145/July 26,1979. Subpart A, Appendix B, p. 44065 - 44066.

Healy, M.J.R. (1972) Animal Litters as Experimental Units. Applied Statistics 21, 155 - 159.

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat

Table: 1 Mortalities

Treatment group	Animal number	Day post-coitum	Observation
Ioxynil 35 mg/kg	87	10	Found dead. Cannibalism rendered post-mortem examination impossible
Ioxynil 35 mg/kg	100	8	Found dead. Cause of death not ascertained.
Ioxynil 35 mg/kg	103	8	Found dead. Cannibalism rendered post-mortem examination impossible
Ioxynil 35 mg/kg	106	8	Found dead. Cannibalism rendered post-mortem examination impossible
Ioxynil 35 mg/kg	109	9	Found dead. Cannibalism rendered post-mortem examination impossible
Ioxynil 35 mg/kg	112	7	Found dead. Cannibalism rendered post-mortem examination impossible

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat

Table : 2.1 Controls : Individual bodyweights of dams with viable young

Animal number	Bodyweights (g) on days post-coitum					
	5	8	11	14	18	22
1	212	224	245	268	301	365
2	208	216	231	249	282	324
3	217	239	260	283	315	361
4	237	251	268	289	327	381
5	213	222	245	265	296	346
6	221	236	251	277	321	361
7	201	210	230	252	286	346
8	224	242	263	285	319	370
9	222	235	260	276	302	345
10	224	243	251	282	323	361
11	189	205	220	239	267	302
12	190	203	224	245	278	337
13	233	245	265	287	321	367
14	236	248	265	282	315	376
15	206	222	235	252	287	332
16	207	219	235	256	286	340
17	183	210	224	246	279	339
18	211	247	266	241	325	384
19	179	211	225	241	253	266
20	191	213	227	247	273	320
21	187	205	217	233	228	303
22	246	262	282	306	318	408
23	241	261	279	305	306	399
24	195	215	234	255	256	332
25	237	256	266	291	314	386
26	233	248	260	289	310	391
27	204	223	237	256	278	346

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat

Table : 2.2 Ioxynil 5 mg/kg : Individual bodyweights of dams with viable young

Animal number	Bodyweights (g) on days post-coitum					
	5	8	11	14	18	22
29	209	218	229	254	289	339
30	200	213	225	246	281	325
31	230	246	264	285	326	390
32	200	215	233	255	287	343
33	225	239	260	274	316	351
34	225	233	251	267	307	337
35	225	238	261	279	323	382
36	229	238	259	275	314	367
37	217	226	238	259	291	340
38	232	236	261	276	307	361
40	190	197	215	231	265	318
41	227	238	256	285	325	367
42	243	259	278	302	338	399
44	236	253	266	292	332	391
45	232	239	255	282	304	354
46	210	213	235	254	289	338
47	193	217	244	275	294	366
49	229	244	264	286	319	368
50	207	224	245	268	304	340
51	203	226	244	266	306	339
52	211	228	244	269	303	344
53	210	226	232	256	274	341
54	239	256	257	294	306	375
55	225	251	252	295	297	350
56	210	226	230	255	266	324

IOXYNIL TECHNICAL: Teratogenicity study by the oral route in the rat

Table: 2.3 Ioxynil 15 mg/kg: Individual bodyweights of dams with viable young

Animal number	Bodyweights (g) on days post-coitum					
	5	8	11	14	18	22
57	223	229	246	271	309	361
58	211	220	229	247	279	317
59	215	228	242	260	295	342
60	212	225	234	254	286	339
61	200	209	231	253	284	348
62	231	239	256	272	315	376
63	193	204	224	236	271	330
64	199	212	230	249	280	345
65	207	219	227	268	284	337
67	217	231	249	278	303	393
68	216	225	236	262	286	349
69	204	209	225	242	260	289
70	231	236	249	272	301	355
71	212	223	247	271	306	372
72	222	229	247	262	301	366
73	201	207	227	248	288	336
74	211	214	230	250	288	347
75	218	220	238	267	266	329
76	203	210	229	243	259	278
77	237	244	265	286	334	381
78	219	222	242	260	292	347
79	195	208	224	241	271	312
80	203	220	238	258	292	348
81	216	224	246	271	292	347
82	222	234	243	275	294	366
83	224	236	245	272	292	365
84	203	214	222	244	267	347

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat

Table : 2.4 Ioxynil 35 mg/kg : Individual bodyweights of dams with viable young

Animal number	Bodyweights (g) on days post-coitum					
	5	8	11	14	18	22
86	232	209	235	260	292	350
87	(227)	(210)	Found dead			
88	190	185	194	215	252	312
89	201	191	211	229	264	308
90	192	181	203	219	245	299
91	212	194	225	236	262	327
92	192	183	202	218	247	292
93	224	210	215	222	224	293
94	207	190	189	214	226	302
95	185	180	181	209	226	287
96	238	221	234	260	274	344
97	178	171	184	204	231	288
98	222	203	234	252	286	331
99	202	201	223	245	287	342
100	(236)	Found dead				
101	177	189	217	241	289	355
103	(200)	Found dead				
105	206	195	208	236	275	279
106	(205)	Found dead				
107	213	202	216	237	277	266
108	227	198	228	232	282	274
109	(232)	(214)	Found dead			
110	218	216	234	261	293	370
111	230	215	234	255	292	369
112	(210)	Found dead				

IOXYNIL TECHNICAL: Teratogenicity study by the oral route in the rat

Table 3.1 Group mean bodyweights of dams with viable young

Treatment Group	Number of Animals	Group mean bodyweight (g) on days post-coitum					
		5	8	11	14	18	22
Control 0 mg/kg	27	213 (4)	230 (4)	247 (4)	267 (4)	295 (5)	351 (6)
Ioxynil 5 mg/kg	25	218 (3)	232 (3)	248 (3)	271 (3)	303 (4)	354 (4)
Ioxynil 15 mg/kg	27	213 (2)	222 (2)	238 (2)	260 (3)	289 (3)	345 (5)
Ioxynil 35 mg/kg	19	208 (4)	197** (3)	214** (4)	234** (4)	264** (6)	315** (7)

Standard error in parenthesis ** $p < 0.01$

IOXYNIL TECHNICAL: Teratogenicity study by the oral route in the rat

Table 3.2 Group mean bodyweight gain (g) 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 0 mg/kg	27	17	34	54	82	138
Ioxynil 5 mg/kg	25	14	30	53	85	136
Ioxynil 15 mg/kg	27	9	25	47	76	132
Ioxynil 35 mg/kg	19	-11	6	26	56	107

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat

Table 4.1 Controls: food consumption of dams

Cage No. \ Day No.	g/rat/day					
	0-5	5-8	8-11	11-14	14-18	18-22
1	16·3	22·3	23·8	24·8	25·5	14·0
2	20·5	22·3	24·0	25·8	27·3	20·0
3	19·3	23·8	37·0	26·5	14·5	26·3
4	18·8	21·0	25·5	23·5	13·8	25·3
5	11·0	20·3	21·3	14·5	24·5	23·8
6	20·5	23·8	24·3	18·8	27·8	27·8
7	20·5	22·8	15·5	27·0	24·0	27·5

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat

Table 4.2 Ioxynil 5 mg/kg: food consumption of dams

Day No. / Cage No.	g/rat/day					
	0-5	5-8	8-11	11-14	14-18	18-22
8	15.5	21.3	22.8	24.5	26.3	14.8
9	22.3	23.5	25.0	26.8	28.3	23.0
10	19.8	21.3	23.0	23.3	13.5	22.3
11	21.8	23.8	24.8	26.0	15.8	28.3
12	13.5	17.3	24.3	11.0	26.0	23.8
13	21.3	24.5	24.8	22.5	26.3	27.0
14	23.3	25.5	10.8	30.0	25.3	30.5

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat

Table 4.3 Ioxynil 15 mg/kg: food consumption of dams.

Cage No. \ Day No.	g/rat/day					
	0-5	5-8	8-11	11-14	14-18	18-22
15	18.3	21.8	22.5	25.3	26.5	13.5
16	19.8	21.0	23.3	26.8	27.3	21.3
17	19.5	24.3	23.0	30.3	20.0	28.8
18	19.3	19.8	23.5	25.3	15.0	29.5
19	19.0	19.0	23.5	11.0	27.0	30.8
20	15.8	20.8	23.8	19.8	24.8	27.3
21	20.8	21.3	10.3	29.3	24.5	30.5

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat

Table 4.4 Ioxynil 35 mg/kg: food consumption of dams

Cage No. \ Day No.	g/rat/day					
	0-5	5-8	8-11	11-14	14-18	18-22
22	20·5	15·0	19·1	24·3	29·7	14·0
23	20·3	14·8	24·3	27·3	28·3	21·0
24	20·3	15·8	22·3	27·0	15·3	31·8
25	19·8	14·0	25·3	27·3	21·0	27·0
26	13·0	9·8	24·0	10·7	28·0	25·3
27	21·3	13·3	24·0	21·7	31·3	20·7
28	20·3	15·3	†6·0	30·5	32·0	34·5

†figure artificially reduced due to cannibalism of two animals.

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat

Table 5 . Group mean food consumption of dams

Group \ Day No.	g/rat/day					
	0-5	5-8	8-11	11-14	14-18	18-22
Control	18.1 (1.3)	22.3 (0.5)	23.9 (2.5)	23.0 (1.8)	22.5 (2.2)	23.5 (1.9)
Ioxynil 5 mg/kg	19.6 (1.4)	22.5 (1.0)	22.2 (1.9)	23.4 (2.3)	23.1 (2.2)	24.2 (1.9)
Ioxynil 15 mg/kg	18.9 (0.6)	21.1 (0.6)	21.5 (1.8)	24.0 (2.5)	23.6 (1.7)	26.0 (2.4)
Ioxynil 35 mg/kg	19.4 (1.1)	*** 14.0 (0.8)	20.7 (2.6)	24.1 (2.5)	26.5 (2.3)	24.9 (2.7)

*** $p < 0.001$

Standard error in parenthesis

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat.

Table 6.1 Controls: Individual litter data

RAT NO.	CORPORA LUTEA	TOTAL IMPLANT-ATIONS	PRE IMPLAN-TATION LOSS %	LIVE FOETUSES			UTERINE DEATHS			POST IMPLAN-TATION LOSS %	REMARKS
				NO	♂/♀	MEAN Wt (g)A	EARLY	LATE	TOTAL		
1	11	10	9	10	4 6	5·8	0	0	0	0	
2	13	12	8	12	5 7	5·1	0	0	0	0	
3	14	14	0	13	6 7	5·0	1	0	1	7	
4	14	15	0	14	5 9	5·5	1	0	1	7	
5	13	11	15	11	5 6	5·3	0	0	0	0	
6	16	16	0	16	9 7	5·2	0	0	0	0	
7	11	11	0	9	2 7	5·6	2	0	2	18	
8	11	11	0	8	2 6	5·6	3	0	3	27	
9	14	9	36	9	4 5	5·6	0	0	0	0	
10	14	14	0	12	6 6	5·6	2	0	2	14	
11	10	10	0	5	2 3	4·9	4	1	5	50	
12	11	10	9	10	3 7	5·7	0	0	0	0	
13	17	16	6	13	8 5	5·1	3	0	3	19	
14	11	11	0	11	8 3	5·7	0	0	0	0	
15	11	11	0	11	6 5	5·7	0	0	0	0	
16	11	11	0	11	8 3	5·2	0	0	0	0	

Table 6.1 (Cont....)

RAT NO.	CORPORA LUTEA	TOTAL IMPLANT-ATIONS	PRE IMPLAN-TATION LOSS %	LIVE FOETUSES				UTERINE DEATHS			POST IMPLAN-TATION LOSS %	REMARKS
				NO	♂	♀	MEAN Wt (g) A	EARLY	LATE	TOTAL		
17	13	13	0	12	7	5	3·1	1	0	1	8	
18	12	12	0	12	8	4	3·7	0	0	0	0	
19	11	1	91	1	1	0	4·6	0	0	0	0	No implants in left horn of uterus
20	11	10	9	9	4	5	3·5	1	0	1	10	
21	17	13	24	12	5	7	5·5	1	0	1	8	
22	10	9	10	9	7	2	5·8	0	0	0	0	
23	11	11	0	10	5	5	5·1	1	0	1	9	
24	10	9	10	7	5	2	5·9	2	0	2	22	
25	13	13	0	13	6	7	5·6	0	0	0	0	
26	12	12	0	12	4	8	5·1	0	0	0	0	
27	13	13	0	11	5	6	5·1	2	0	2	15	
28												No visible implants

A = Method A

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat.

Table 6.2 Ioxynil 5 mg/kg : Individual litter data

RAT NO	CORPORA LUTEA	TOTAL IMPLANT-ATIONS	PRE IMPLAN-TATION LOSS %	LIVE FOETUSES			UTERINE DEATHS			POST IMPLAN-TATION LOSS %	REMARKS
				NO	♂ / ♀	MEAN Wt (g) A	EARLY	LATE	TOTAL		
29	11	11	0	10	5 5	5·4	0	1	1	9	
30	12	10	17	10	3 7	4·9	0	0	0	0	
31	12	12	0	12	5 7	5·4	0	0	0	0	
32	12	10	17	10	4 6	5·2	0	0	0	0	
33	14	14	0	14	5 9	4·7	0	0	0	0	
34	15	15	0	14	10 4	5·2	1	0	1	7	
35	17	15	12	15	5 10	5·0	0	0	0	0	
36	14	13	7	13	8 5	5·2	0	0	0	0	
37	15	14	7	13	6 7	5·1	1	0	1	7	
38	13	12	8	10	4 6	5·1	2	0	2	17	
40	13	13	0	13	6 7	5·1	0	0	0	0	
41	12	12	0	11	6 5	5·9	1	0	1	8	

Table 6.2 (Cont....)

RAT NO.	CORPORA LUTEA	TOTAL IMPLANT-ATIONS	PRE IMPLAN-TATION LOSS %	LIVE FOETUSES			UTERINE DEATHS			POST IMPLAN-TATION LOSS %	REMARKS
				NO	♂/♀	MEAN Wt (g)A	EARLY	LATE	TOTAL		
42	14	13	7	13	6 7	5·4	0	0	0	0	
44	16	15	6	15	9 6	5·4	0	0	0	0	
45	9	9	0	9	4 5	3·3	0	0	0	0	No implants in right horn of uterus
46	13	12	8	12	6 6	3·3	0	0	0	0	
47	15	15	0	15	8 7	3.5	0	0	0	0	
49	13	13	0	12	7 5	3·3	1	0	1	8	
50	12	11	8	10	4 6	5·5	1	0	1	9	
51	11	6	45	6	2 4	5·8	0	0	0	0	
52	13	12	8	12	4 8	5·1	0	0	0	0	
53	13	13	0	11	6 5	5.4	2	0	2	15	
54	12	8	33	5	4 1	5·5	3	0	3	38	
55	13	12	8	11	6 5	5·1	1	0	1	8	
56	10	9	10	9	5 4	5·3	0	0	0	0	
39										No visible implants	
43										No visible implants	
48										No visible implants	

A = Method A

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat.

Table 6.3 Ioxynil 15 mg/kg : Individual litter data

RAT NO	CORPORA LUTEA	TOTAL IMPLANT-ATIONS	PRE IMPLAN-TATION LOSS %	LIVE FOETUSES			UTERINE DEATHS			POST IMPLAN-TATION LOSS %	REMARKS
				NO	♂/♀	MEAN Wt (g)A	EARLY	LATE	TOTAL		
57	14	14	0	14	9 5	5·1	0	0	0	0	
58	14	13	7	13	7 6	4·6	0	0	0	0	
59	12	12	0	12	9 3	5·2	0	0	0	0	
60	10	10	0	10	7 3	5·4	0	0	0	0	
61	16	13	19	13	7 6	5·1	0	0	0	0	
62	14	14	0	12	5 7	5·4	1	1	2	14	
63	17	12	29	12	5 7	5·5	0	0	0	0	
64	10	10	0	10	7 3	6·1	0	0	0	0	
65	14	11	21	10	4 6	5·9	1	0	1	9	
67	13	13	0	12	7 5	5·5	1	0	1	8	
68	12	12	0	12	8 4	5·0	0	0	0	0	
69	4	2	50	2	1 1	5·9	0	0	0	0	
70	14	13	7	12	3 9	4·7	1	0	1	8	

Table 6.3 (Cont.....)

RAT NO.	CORPORA LUTEA	TOTAL IMPLANTATIONS	PRE IMPLANTATION LOSS %	LIVE FOETUSES			UTERINE DEATHS			POST IMPLANTATION LOSS %	REMARKS
				NO	♂/♀	MEAN Wt (g)	EARLY	LATE	TOTAL		
71	13	13	0	13	10 3	5·2	0	0	0	0	
72	14	14		13	8 5	5·1	1	0	1	7	
73	12	12	0	12	5 7	2·9	0	0	0	0	
74	12	12	0	12	4 8	3·6	0	0	0	0	
75	11	11	0	11	8 3	3·3	0	0	0	0	
76	4	1	75	1	0 1	3·9	0	0	0	0	No implants in left horn of uterus
77	16	15	6	15	6 9	5·3	0	0	0	0	
78	12	11	8	11	7 4	5.0	0	0	0	0	
79	12	11	8	10	3 7	5.0	1	0	1		
80	11	8	27	7	4 3	5.6	1	0	1	13	
81	13	13	0	12	5 7	5·4	1	0	1	8	
82	14	14	0	14	9 5	4·8	0	0	0	0	
83	11	12	0	12	6 6	5.0	0	0	0	0	

Table 6.3 (Cont.....)

RAT NO.	CORPORA LUTEA	TOTAL IMPLANT-ATIONS	PRE IMPLAN-TATION LOSS %	LIVE FOETUSES			UTERINE DEATHS			POST IMPLAN-TATION LOSS %	REMARKS
				NO.	♂/♀	MEAN Wt (g)A	EARLY	LATE	TOTAL		
84	12	12	0	11	7 4	5·6	1	0	1	8	
66											No visible implants

A = Method A

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat.

Table 6.4 Ioxynil 35 mg/kg : Individual litter data

RAT NO.	CORPORA LUTEA	TOTAL IMPLANT-ATIONS	PRE IMPLAN-TATION LOSS %	LIVE FOETUSES			UTERINE DEATHS			POST IMPLAN-TATION LOSS %	REMARKS
				NO	♂/♀	MEAN Wt (g)A	EARLY	LATE	TOTAL		
86	15	13	13	12	9 3	4·7	1	0	1	8	
88	11	9	18	9	4 5	5·4	0	0	0	0	
89	14	11	21	11	6 5	4·9	0	0	0	0	
90	11	11	0	10	7 3	5·0	1	0	1	9	
91	14	13	7	12	8 4	5·0	0	1	1	8	
92	9	9	0	9	6 3	5·2	0	0	0	0	
93	13	11	15	10	5 5	3·7	0	1	1	9	
94	15	12	20	12	6 6	4·6	0	0	0	0	
95	14	12	14	11	5 6	4·6	1	0	1	8	
96	16	16	0	14	8 6	4·4	2	0	2	13	
97	11	11	0	11	7 4	4·7	0	0	0	0	
98	16	15	6	14	5 9	4·5	1	0	1	7	
99	17	16	6	16	11 5	5·1	0	0	0	0	

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Table 6.4 (Cont.....)

RAT NO.	CORPORA LUTEA	TOTAL IMPLANT-ATIONS	PRE IMPLAN-TATION LOSS %	LIVE FOETUSES			UTERINE DEATHS			POST IMPLAN-TATION LOSS %	REMARKS
				NO	♂/♀	MEAN Wt (g)A	EARLY	LATE	TOTAL		
101	15	13	13	13	7 6	3·4	0	0	0	0	
105	16	14	13	13	7 6	4·3	1	0	1	7	
107	10	10	0	10	3 7	4·7	0	0	0	0	
108	11	11	0	11	6 5	4·4	0	0	0	0	
110	13	13	0	13	5 8	4·8	0	0	0	0	
111	15	14	7	14	7 7	4·8	0	0	0	0	
85											no visible implants
102											no visible implants
104											no visible implants
87											found dead day 10 post-coitum
100											found dead day 8 post-coitum
103											found dead day 8 post-coitum
106											found dead day 8 post-coitum
109											found dead day 9 post-coitum
112											found dead day 7 post-coitum

A = Method A

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IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat.

Table 7

GROUP MEAN LITTER DATA

Group	No. of animals per group	No. pregnant	No. of litters used in statistical analysis	Corpora lutea: mean no/ animal	Implantations: mean no/ animal	Mean pre-implantation loss %	Total no.	Live foetuses					Uterine deaths			Mean post-implantation loss %
								mean no./ animal	no. males	no. females	♂/♀	mean wt. (g) B	Total no.	early deaths	late deaths	
Control 0 mg/kg	28	27	27	12.4 (0.4)	11.4 (0.6)	8.4	283	10.5 (0.6)	140	143	1.0	5.4 ††	25	24	1	7.9
Ioxynil 5 mg/kg	28	25	25	13.0 (0.4)	12.0 (0.5)	8.0	285	11.4 (0.5)	138	147	0.9	5.3 †††	14	13	1	5.0
Ioxynil 15 mg/kg	28	27	27	12.3 (0.6)	11.4 (0.6)	9.5	298	11.0 (0.6)	161	137	1.2	5.3 ‡	10	9	1	3.1
Ioxynil 35 mg/kg	28	19 †	19	13.5 (0.5)	12.3 (0.5)	8.1	225	11.8 (0.4)	128	105	1.2	4.7 *** □	9	7	2	3.6

Standard error in parenthesis

†Six animals died during the dosing period. Cannibalism rendered examination impossible, and no pregnancy data are available

†† Data from litters 17, 18, 19 and 20 excluded.

††† Data from litters 45, 46 and 47 excluded.

‡ Data from litters 73, 74, 75 and 76 excluded.

□ Data from litter 101 excluded.

B = Method B

*** $p < 0.001$

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IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Table 8.1 Control : Foetal examination (major malformation & minor anomaly)

Female No.	Number of young				
	No. examined	Major malformations		Minor anomalies	
		No.	Description	No.	Description
† 1	10	0		1	Unilateral left hydroureter.
				1	Bilateral hydroureter; left kidney increased renal pelvic cavitation.
2	12	0		0	
3	13	0		1	Absent ossification of 5th sternebra.
†† 4	14	0		0	
5	11	0		0	
6	16	0		2	Bilateral hydroureter.
7	9	0		0	
8	8	1	Hydrocephalus	0	
9	9	0		1	Bipartite 5th sternebra.
10	12	0		1	Increased size of anterior fontanelle. Proximal phalanges in each forelimb ossification absent.
				1	Proximal phalanges in each forelimb ossification absent.
				2	Increased size of anterior fontanelle.
11	5	0		0	
12	10	0		0	

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Table 8.1 Control : Foetal examination (major malformation & minor anomaly) (cont.)

Female No.	Number of young				
	No. examined	Major malformations		Minor anomalies	
		No.	Description	No.	Description
13	13	0		1	Bipartite 11th thoracic vertebral centrum.
				1	Bipartite 5th sternebra. Absent ossification 6th sternebra.
				1	Absent ossification 6th sternebra. Only 3 metacarpals ossified in each forelimb. Proximal phalanges in each forelimb ossification absent
14	11	0		1	Bipartite 5th thoracic vertebral centrum
				1	Proximal phalanges in each forelimb ossification absent.
15	11	0		1	Absent ossification 5th sternebra.
16	11	0		1	Absent ossification of 5th sternebra.
				1	Proximal phalanges in each forelimb ossification absent.
				1	Bipartite 12th thoracic vertebral centrum.
21	12	0		0	
22	9	0		0	
23	10	0		0	
24	7	0		0	

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Table 8.1 (cont.) Control : Foetal examination (major malformation & minor anomaly)

Female No.	Number of young				
	No. examined	Major malformations		Minor anomalies	
		No.	Description	No.	Description
25	13	0		1	Kidney:- Bilateral subcapsular haematoma.
26	12	0		0	
27	11	0		1	13th rib left hand side reduced ossification.

† 1 pup missing
†† Frontals and parietals removed at dissection and discarded in error.

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Table 8.2 Control: Foetal examination (major malformation & minor anomaly)
Animals considered not to be day 22 post-coitum

Female No.	Number of young				
	No. examined	Major malformations		Minor anomalies	
		No.	Description	No.	Description
† 17	12	0		3	Absent ossification 5th sternebra. Only 3 metacarpals ossified in each forelimb. Proximal phalanges in each forelimb ossification absent.
				1	Absent ossification of 5th sternebra.
				1	Absent ossification of hyoid body. Proximal phalanges in each forelimb ossification absent.
				2	Absent ossification of 5th and 6th sternebrae. Absent ossification of hyoid body. Proximal phalanges in each forelimb ossification absent. Only 3 metacarpals ossified in each forelimb.
				3	Absent ossification of 5th sternebra. Absent ossification of hyoid body. Proximal phalanges in each forelimb ossification absent. Only 3 metacarpals ossified in each forelimb.
				1	Absent ossification of hyoid body. Proximal phalanges in each forelimb ossification absent

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Table 8.2 Control: Foetal examination (major malformation & minor anomaly) (cont.)
Animals considered not to be day 22 post-coitum

Female No.	Number of young				
	No. examined	Major malformations		Minor anomalies	
		No.	Description	No.	Description
17 (cont.)				(cont.)	Only 3 metacarpals ossified in each forelimb.
				1	Absent ossification of 5th sternebra. Proximal phalanges in each forelimb ossification absent.
† 18	12	0		6	Proximal phalanges in each forelimb ossification absent.
				1	Proximal phalanges in each forelimb ossification absent. Only 3 metacarpals ossified in each forelimb.
† 19	1	0		0	
† 20	9	0		5	Proximal phalanges in each forelimb ossification absent. Only 3 metacarpals ossified in each forelimb.
				1	Absent ossification of 5th sternebra. Only 3 metacarpals ossified in each forelimb.
				1	Absent ossification of 5th sternebra. Proximal phalanges in each forelimb ossification absent. Only 3 metacarpals ossified in each forelimb.

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Table 8.2 Control : Foetal examination (major malformation & minor anomaly)
(cont.) Animals considered not to be day 22 post-coitum

Female No.	Number of young				
	No. examined	Major malformations		Minor anomalies	
		No.	Description	No.	Description
20 (cont.)				1	Only 3 metacarpals ossified in each forelimb.

† Foetal weight and degree of ossification indicates that these litters are not day 22 post-coitum. Data excluded from group means.

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Table 8.3 5mg/kg : Foetal examination (major malformation & minor anomaly)

Female No.	Number of young				
	No. examined	Major malformations		Minor anomalies	
		No.	Description	No.	Description
†† 29	10	0		0	
†† 30	10	0		0	
31	12	0		0	
†† 32	10	0		1	Absent ossification of 5th sternebra Bipartite 3rd and 4th sternebrae.
33	14	0		0	
34	14	0		0	
35	15	0		0	
36	13	0		0	
37	13	0		0	
38	10	0		1	Absent ossification of 5th sternebra.
				1	Proximal phalanges in each forelimb ossification absent.
				1	Absent ossification of 5th stenebra. Proximal phalanges in each forelimb ossification absent.
40	13	0		1	Left 13th rib reduced ossification to ½ normal length.
41	11	0		0	

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Table 8.3 (cont.) 5 mg/kg : Foetal examination (major malformation & minor anomaly)

Female No.	Number of young				
	No. examined	Major malformations		Minor anomalies	
		No.	Description	No.	Description
42	13	0		1	Bipartite 11th thoracic vertebral centrum.
44	15	0		1	Bipartite 11th thoracic vertebral centrum.
49	12	0		2	Absent ossification of hyoid body.
50	10	0		0	
51	6	0		1	Bipartite 12th thoracic vertebral centrum and 1st lumbar vertebral centrum.
52	12	0		0	
53	11	0		0	
54	5	0		0	
55	11	0		2	Bilateral hydroureter
				2	Absent ossification 5th sternebra.
56	9	0		1	13th ribs slightly reduced.

†† Frontals and parietals removed at dissection and discarded in error

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Table 8.4 5 mg/kg : Foetal examination (major malformation & minor anomaly)
Animals considered not to be day 22 post-coitum

Female No.	Number of young				
	No. examined	Major malformations		Minor anomalies	
		No.	Description	No.	Description
† 45	9	0		3	Absent ossification of 5th and 6th sternebrae. Proximal phalanges in each forelimb ossification absent. Only 3 metacarpals ossified in each forelimb.
				5	Proximal phalanges in each forelimb ossification absent Only 3 metacarpals ossified in each forelimb.
				1	Absent ossification of 5th and 6th sternebrae. Absent ossification of hyoid body. Only 2 caudal vertebrae ossified. Proximal phalanges in each forelimb ossification absent. Only 3 metacarpals ossified in each forelimb.
† 46	12	0		1	Only 3 metacarpals ossified in each forelimb.
				5	Proximal phalanges in each forelimb ossification absent Only 3 metacarpals ossified in each forelimb.

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Table 8.4 (cont.) 5 mg/kg : Foetal examination (major malformation & minor anomaly)
Animals considered not to be day 22 post-coitum

Female No.	Number of young				
	No. examined	Major malformations		Minor anomalies	
		No.	Description	No.	Description
46 (Cont)				1	Absent ossification of hyoid body. Proximal phalanges in each forelimb ossification absent. Only 3 metacarpals ossified in each forelimb.
				2	Absent ossification 5th sternebra. Proximal phalanges in each forelimb ossification absent. Only 3 metacarpals ossified in each forelimb.
				1	Absent ossification of 5th & 6th sternebrae. Proximal phalanges in each forelimb ossification absent. Only 3 metacarpals ossified in each forelimb.
				1	Absent ossification of 2nd, 5th and 6th sternebrae.

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Table 8.4 (Cont.) 5 mg/kg : Foetal examination (major malformation & minor anomaly

Animals considered not to be day 22 post-coitum

Female No.	Number of young				
	No. examined	Major malformation		Minor anomalies	
		No.	Description	No.	Description
46 (Cont.)				Cont-	Absent ossification of hyoid body. Proximal phalanges in each forelimb ossification absent. Only 3 metacarpals ossified in right forelimb (left forepaw lost during processing).
				1	Absent ossification of 6th sternebra. Proximal phalanges in each forelimb ossification absent. Only 3 metacarpals ossified in each forelimb.
†47	15	0		1	Absent ossification of 5th sternebra. Proximal phalanges in each forelimb ossification absent.
				1	Absent ossification of of 5th and 6th sternbrae. Proximal phalanges in each forelimb ossification absent. Only 3 metacarpals ossified in each forelimb.

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Table 8.4 (Cont.) 5 mg/kg : Foetal examination (major malformation & minor anomaly

Animals considered not to be day 22 post-coitum

Female No.	Number of young				
	No. examined	Major malformations		Minor anomalies	
		No.	Description	No.	Description
47 (Cont.)	15	Cont.		4	Proximal phalanges in each forelimb ossification absent. Only 3 metacarpals ossified in each forelimb.
				5	Proximal phalanges in each forelimb ossification absent.
				1	Proximal phalanges in left forelimb ossification absent (right forepaw lost during processing).

† Foetal weight and degree of ossification indicates that these litters are not day 22 post-coitum. Data excluded from group means.

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Table 8.5 15 mg/kg: Foetal examination (major malformation & minor anomaly)

Female No.	Number of young				
	No. examined	Major malformations		Minor anomalies	
		No.	Description	No.	Description
57	14	0		0	
‡‡ 58	13	0		1	Absent ossification 5th sternebra and proximal phalanges in each forelimb. Only 3 metacarpals ossified in each forelimb.
				2	Absent ossification hyoid body.
‡‡ 59	12	0		0	
‡‡ 60	10	0		0	
61	13	0		1	13th rib, left side reduced to half normal length.
				1	Absent ossification proximal phalanges in each forelimb.
62	12	0		0	
63	12	0		0	
64	10	0		1	Bilateral hydroureter.
				1	Bipartite 13th thoracic vertebral centrum.
				1	Absent ossification hyoid body.
65	10	0		0	
67	12	0		1	Absent ossification proximal phalanges in each forelimb.
		1	Absence of thymus		

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Table 8.5 15 mg/kg: Foetal examination (major malformation & minor anomaly) (cont.)

Female No.	Number of young				
	No. examined	Major malformations		Minor anomalies	
		No.	Description	No.	Description
68	12	0		0	
69	2	0		1	Blood suffused iris left eye.
70	12	1	Imperforate anus	1	Only 3 bipartite sternebrae ossified. Absent ossification 1st thoracic vertebral centrum. Bipartite 8th, 9th thoracic vertebral centra and 1st, 2nd and 5th lumbar vertebral centra. Only 3 metacarpals ossified in each forelimb.
71	13	0		3	Absent ossification proximal phalanges in each forelimb.
				1	Bipartite 10th thoracic vertebral centrum.
72	13	0		0	
77	15	0		3	Absent ossification proximal phalanges in each forelimb.
				1	Absent ossification proximal phalanges in each forelimb. Only 3 metacarpals ossified in each forelimb.
				1	Absent ossification hyoid body.

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Table 8.5 15 mg/kg: Foetal examination (major malformation & minor anomaly) (cont.)

Female No.	Number of young				
	No. examined	Major malformations		Minor anomalies	
		No.	Description	No.	Description
78	11	0		1	Bipartite 5th sternebra.
				2	Absent ossification hyoid body.
				1	Bipartite 12th thoracic vertebral centrum.
79	10	0		0	
80	7	0		0	
81	12	0		2	Absent ossification proximal phalanges in each forelimb.
82	14	0		0	
83	12	0		0	
84	11	0		0	

†† Frontals and parietals removed at dissection and discarded in error.

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Table 8.6 15 mg/kg: Foetal examination (major malformation & minor anomaly)
Animals considered not to be day 22 post-coitum

Female No.	Number of young				
	No. examined	Major malformations		Minor anomalies	
		No.	Description	No.	Description
† 73	12	0		5	Absent ossification proximal phalanges in each forelimb. Only 3 metacarpals ossified in each forelimb.
				3	Absent ossification 5th sternebra Absent ossification proximal phalanges in each forelimb. Only 3 metacarpals ossified in each forelimb.
				2	Absent ossification 5th & 6th sternebrae and proximal phalanges in each forelimb. Only 3 metacarpals ossified in each forelimb.
				1	Bilateral hydroureter Absent ossification proximal phalanges in each forelimb. Only 3 metacarpals ossified in each forelimb.
				1	Absent ossification 2nd sternebra. Absent ossification proximal phalanges in each forelimb. Only 3 metacarpals ossified in each forelimb.

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Table 8.6 (Cont.) 15 mg/kg: Foetal examination (major malformation & minor anomaly)
Animals considered not to be day 22 post-coitum

Female No.	Number of young				
	No. examined	Major malformations		Minor anomalies	
		No.	Description	No.	Description
† 74	12	0		5	Absent ossification proximal phalanges in each forelimb. Only 3 metacarpals ossified in each forelimb.
				3	Absent ossification 5th sternebra and proximal phalanges in each forelimb.
				3	Absent ossification proximal phalanges in each forelimb.
† 75	11	0		3	Absent ossification 5th and 6th sternebrae. Only 3 metacarpals ossified in each forelimb.
				3	Absent ossification 5th and 6th sternebrae and proximal phalanges in each forelimb. Only 3 metacarpals ossified in each forelimb.
				2	Absent ossification proximal phalanges in each forelimb. Only 3 metacarpals ossified in each forelimb.
				1	Absent ossification 6th sternebra and proximal phalanges in each forelimb. Only 3 metacarpals ossified in each forelimb.

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Table 8.6 (Cont.) 15 mg/kg: Foetal examination (major malformation & minor anomaly)
Animals considered not to be day 22 post-coitum

Female No.	Number of young				
	No. examined	Major malformations		Minor anomalies	
		No.	Description	No.	Description
75 Cont.				1	Bipartite and incomplete ossification 5th sternebra. Absent ossification 6th sternebra and proximal phalanges in each forelimb. Only 3 metacarpals ossified in each forelimb.
				1	Absent ossification 6th sternebra. Only 3 metacarpals ossified in each forelimb.
† 76	1	0		1	Absent ossification proximal phalanges in each forelimb. Only 3 metacarpals ossified in each forelimb. Unilateral right hydroureter & increased renal pelvic cavitation (right kidney).

† Foetal weight and degree of ossification indicates that these litters are not day 22 post-coitum. Data excluded from group means.

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Table 8.7 35 mg/kg:Foetal examination (major malformation & minor anomaly)

Female No.	Number of young				
	No. examined	Major malformations		Minor anomalies	
		No.	Description	No.	Description
86	12	0		2	Bilateral hydroureter Proximal phalanges in each forelimb ossification absent.
				3	Bilateral hydroureter.
				1	Unilateral left hydroureter.
88	9	0		2	Bilateral hydroureter
				1	Bilateral hydroureter. Unilateral left renal pelvic cavitation.
				1	Bipartite 5th thoracic vertebral centrum. Incomplete ossification of 8th thoracic vertebral centrum, displaced to animals left. 9th thoracic vertebral centrum malformed. 8th and 9th ribs right hand side fused at capitulae
89	11	0		1	Bilateral hydroureter. Bilateral increased renal pelvic cavitation
				1	Unilateral left hydroureter.
				1	Bilateral hydroureter.
90	10	0		1	Bilateral hydroureter Proximal phalanges in each forelimb , ossification absent.

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Table 8.7 35 mg/kg : Foetal examination (major malformation & minor anomaly) (Cont..)

Female No.	Number of young				
	No. examined	Major malformations		Minor anomalies	
		No.	Description	No.	Description
90 Cont.				1	Proximal phalanges in each forelimb ossification absent
				1	Proximal phalanges left forelimb ossification absent.
91	12	0		3	Bilateral hydroureter
				1	Absent ossification of 5th sternebra.
92	9	0		4	Bilateral hydroureter
93	10	0		2	Proximal phalanges in each forelimb ossification absent.
				1	13th rib right hand-side reduced ossification.
				1	Bipartite 2nd sternebra Absent 5th sternebra Proximal phalanges in each forelimb ossification absent.
				1	Proximal phalanges in each forelimb ossification absent. Only 3 metacarpals ossified in each forelimb.
				1	Bipartite 5th sternebra Proximal phalanges in each forelimb ossification absent.
94	12	0		0	

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Table 8.7 35 mg/kg : Foetal examination (major malformation & minor anomaly) (Cont..)

Female No.	Number of young				
	No. examined	Major malformations		Minor anomalies	
		No.	Description	No.	Description
95	11	0		1	Proximal phalanges in each forelimb ossification absent. Only 3 metacarpals ossified in each forelimb. 1st and 2nd thoracic vertebral centra absent. 11th and 13th thoracic vertebral centra bipartite. 7th and 8th ribs left hand side fused at capitulae. 11th and 12th ribs fused distal to capitulae left hand side. 3rd and 4th sternebrae bipartite, 5th sternebrae ossification absent. Increased size of anterior fontanelle. Only 3 caudal vertebrae ossified.
96	14	0		1	Bilateral hydroureter Proximal phalanges in each forelimb ossification absent.
				1	Bilateral hydroureter
				2	Proximal phalanges in each forelimb ossification absent.

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Table 8.7 35 mg/kg : Foetal examination (major malformation & minor anomaly) (Cont..)

Female No.	Number of young				
	No. examined	Major malformations		Minor anomalies	
		No.		No.	Description
97	11	0		2	Bilateral hydroureter
98	14	0			
99	16	1	Both kidneys rudimentary-reduced to 1 mm in length		1st, 2nd, 3rd sternebrae fused. Absent ossification of 2nd thoracic vertebral centrum. 10th thoracic vertebral centrum incompletely ossified and bipartite. Only 3 metacarpals ossified in each forelimb. Proximal phalanges in each forelimb ossification absent. Only 4 distal phalanges present in each forelimb. Only 4 digits present in each forelimb. Only 4 distal phalanges ossified in each hindlimb. Incomplete and irregular ossification 3rd, 4th, 5th, 6th, 7th, 8th, 9th thoracic vertebral centra.
				1	Bilateral hydroureter.
				2	Bipartite 12th thoracic vertebral centrum.
105	13	0		2	Both kidneys sub-capsular haematoma.
				1	Bilateral hydroureter.
				1	5th sternebra bipartite and reduced.

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Table 8.7 35 mg/kg : Foetal examination (major malformation & minor anomaly)
(Cont..)

Female No.	Number of young				
	No. examined	Major malformations		Minor anomalies	
		No.	Description	No.	Description
107	10	0		1	Bilateral hydroureter.
				2	Absent ossification of hyoid body.
				1	Proximal phalanges in each forelimb ossification absent.
				1	Absent ossification of hyoid body. Proximal phalanges in each forelimb ossification absent
108	11	0		1	1st lumbar vertebral centrum bipartite.
110	13	0		2	Proximal phalanges in each forelimb ossification absent.
111	14	0		0	

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Table 8.8 35 mg/kg : Foetal examination (major malformation & minor anomaly)
Animals considered not to be day 22 post-coitum

Female No.	Number of young				
	No examined	Major malformations		Minor anomalies	
		No.	Description	No.	Description
†101	13	0		3	Only 3 metacarpals ossified in left forelimb
				4	Absent ossification 6th stenebra. Proximal phalanges in each forelimb ossification absent. Only 3 metacarpals ossified in each forelimb .
				4	Proximal phalanges in each forelimb absent ossification. Only 3 metacarpals ossified in each forelimb .

†Foetal weight and degree of ossification indicates that this litter is not day 22 post-coitum. Data excluded from group means.

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Foetal examination (major malformation and minor anomaly)

Table 9

Treatment Group	Number of young				
	No. examined	Major malformations		ϕ Minor anomalies	
		Total number	Mean % C	Total number	Mean % C
† Control	249	1	0·5	21	7·8
†† Ioxynil 5 mg/kg	249	0	0	15	6·5
††† Ioxynil 15 mg/kg	262	2	0·7	25	10·6
‡ Ioxynil 35 mg/kg	212	1	0·3	52	** 26.1

ϕ young showing major malformations excluded

C = method C 2.6.3

† Data from litters 17, 18, 19 and 20 excluded

†† Data from litters 45, 46 and 47 excluded

††† Data from litters 73, 74, 75 and 76 excluded

‡ Data from litters 101 excluded

** $p < 0.01$

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Table 10·1 Foetal examination. Incidence of hydroureter

	Control	5 mg/kg Ioxynil	15 mg/kg Ioxynil	35 mg/kg Ioxynil
No. of foetuses examined	283	285	298	225
No. of foetuses exhibiting bilateral hydroureter	3	2	2	25**
Percentage of foetuses exhibiting bilateral hydroureter	1·06	0·70	0·67	11·11
No. of foetuses exhibiting unilateral left hydroureter	1	0	0	2
No. of foetuses exhibiting unilateral right hydroureter	0	0	1	0
Total no. of foetuses with hydroureter	4	2	3	27**
Percentage of foetuses with hydroureter	1·41	0·70	1·01	12·00
Bilateral increased renal pelvic cavitation	0	0	0	1
Unilateral left increased renal pelvic cavitation.	1	0	0	1
Unilateral right increased renal pelvic cavitation.	0	0	1	0
Total increased renal pelvic cavitation	1	0	1	2

* $p < 0.05$
** $p < 0.01$

Data includes observations from litters found not to be day 22 post-coitum at necropsy and skeletal examination.

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat
Table 10·2 Foetal examination. Incidence of supernumerary rib variants

	Control	5 mg/kg Ioxynil	15 mg/kg Ioxynil	35 mg/kg Ioxynil
No. of foetuses examined	†282	285	298	225
Bilateral 14th rib ossification reduced	2	8	* 22	** 46
Percentage bilateral 14th rib ossification reduced	0·71	2·81	7·38	20·44
Unilateral left 14th rib ossification reduced	4	9	* 15	** 21
Percentage unilateral left 14th rib ossification reduced	1·42	3·16	5·03	9·33
Unilateral right 14th rib ossification reduced	0	4	2	11
Percentage, unilateral right 14th rib ossification reduced	0	1·40	0·67	4·89
Bilateral 14th rib, right normal ossification, left ossification reduced	0	2	0	3
Bilateral 14th rib, left normal ossification, right ossification reduced	0	0	1	3
Bilateral 14th rib ossification normal	0	0	0	5
Total no. of rib variants	6	23	** 40	*** 89
Percentage of foetuses with rib variants	2·13	8·07	13·42	39·56

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

† 1 pup missing from skeletal examination.

Data includes observations from litters found not to be day 22 post-coitum at necropsy and skeletal examination.

FIGURE I

Ioxynil technical.

Teratogenicity study by the oral route in the rat

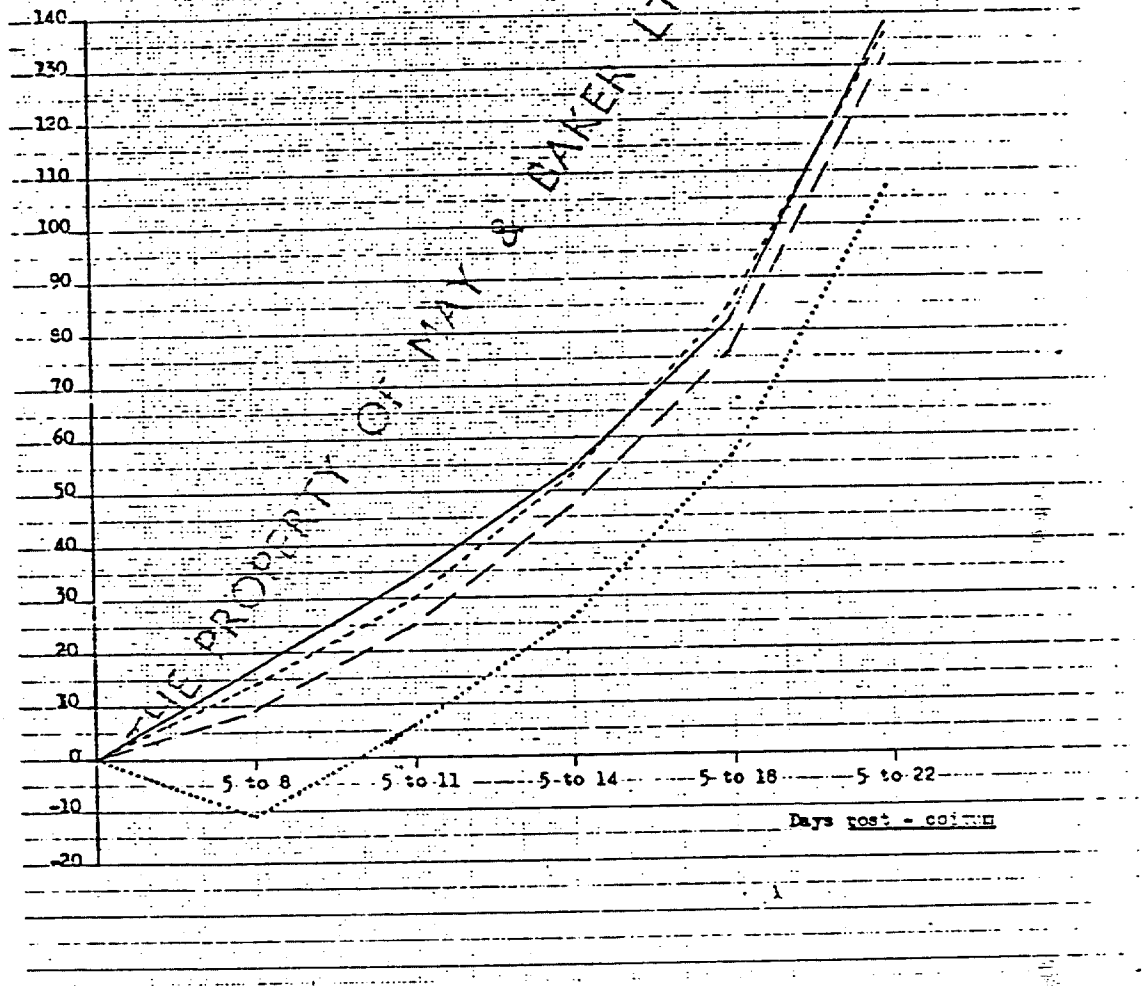
Group mean bodyweight gain days 5 to 22 post coitum.

0 mg/kg ioxynil technical

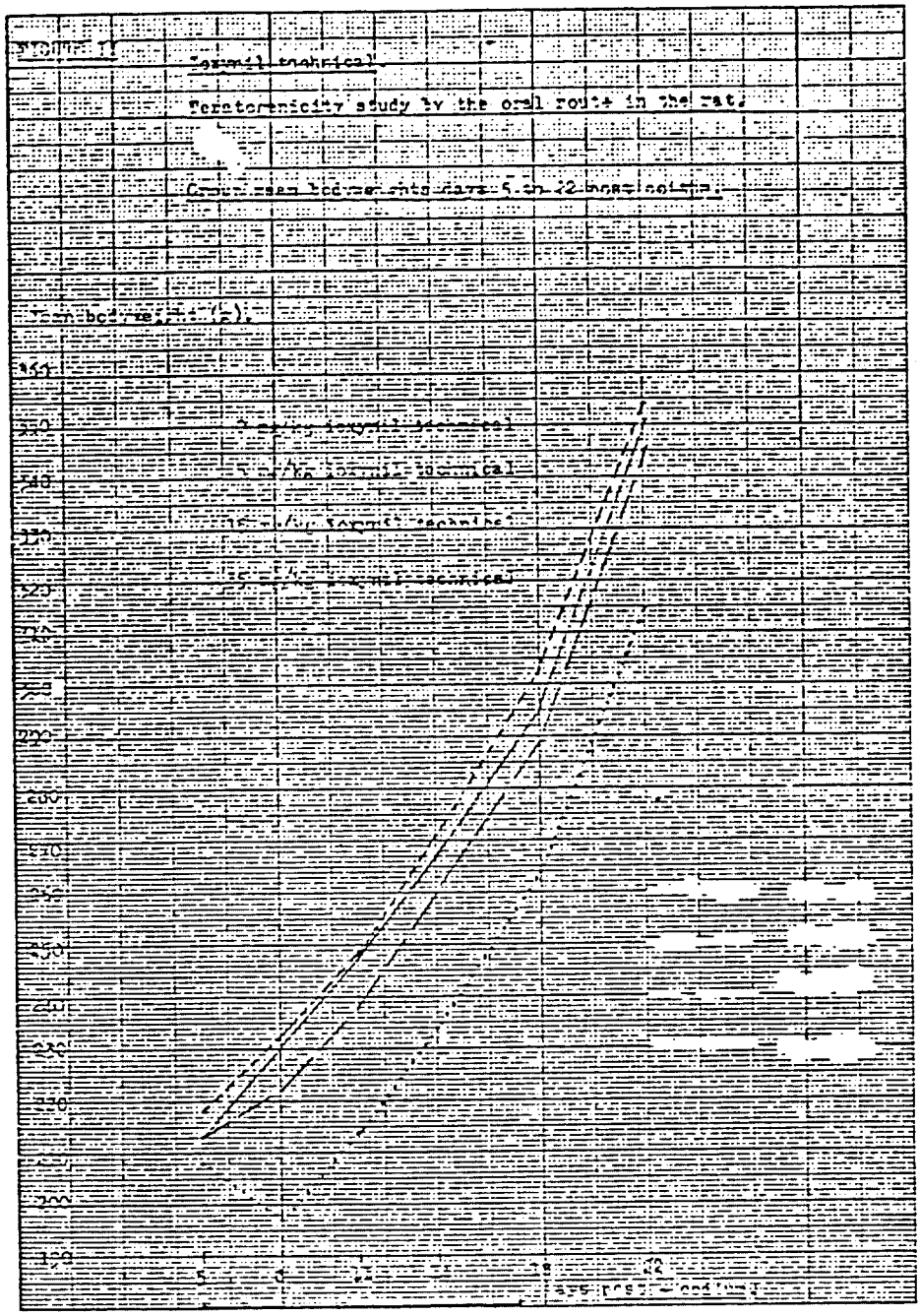
5 mg/kg ioxynil technical

15 mg/kg ioxynil technical

35 mg/kg ioxynil technical



64/08/25



Signature: Copping

Name: G. P. Copping

Qualification: H.N.D.

Appointment: Reproductive Toxicology Unit Head

Work carried out at: Research Laboratories
May & Baker Ltd.,
Dagenham.

Date: 10/February/1981

Signature:

Name:

Qualification:

Appointment:

Work carried out at:

Date:

QUALITY ASSURANCE AUTHENTICATION

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat

(R.Tox. 12)

The study reported here was inspected on the following dates :

19 and 26 September 1980,
3, 7, 9, 16, 19, 26 and 30 October 1980,
12 and 18 November 1980,
11 and 16 December 1980, and
6 February 1981.

The findings of these inspections were reported to the Line Managers on 6 February 1981.

This report was audited by Research Documentation and Auditing Department on 18 February 1981, and has been found to describe accurately the methods and SOP's used. The results also accurately reflect the raw data from the study.

D.L. Colinese
Quality Assurance Unit

Dated 18 February 1981

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat.

Appendix I

May & Baker Ltd
Pharmaceutical and Chemical Manufacturers

Sweet Briar Road
Norwich NR6 5AP
Telegrams: Bismuth Norwich
Telex: Norwich 97152
Telephone: (0603) 47373

Our ref: BJF/4G Your ref: Date: 7.3.79.

ANALYTICAL REPORT

IOXYNIL TECHNICAL (DAMP)

Batch No: KN 503

Appearance	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 dim.
	b) A 5% solution of dried material in acetone is complete.
Melting Point	203.9°C determined on the dried material.
Inorganic Iodides	0.02% as I.
Sulphated Ash	0.02%.
Loss on Drying	About 1% at 105°C.
Related Impurities	3.1% w/v.
Assay	
a) Based on iodine	98.7% calculated with reference to the dried material.
b) By G.C.	98.2% determined on the dried material.
Mineral Acid Content	Negligible.

B.J. Ferrier, C.Chem., M.R.I.C.,
Quality Control - Norwich.

IOXYNIL TECHNICAL : Teratogenicity study by the oral route in the rat.

Appendix II

Dr. BERNARD DYER and PARTNERS (1948) Ltd.

DIRECTORS
Dr. J. H. HAMENCE, B.Sc., C.Chem., F.R.I.C.
P. B. HALL, C.Chem., F.R.I.C.
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TELEPHONE—01-626 6934
TELEGRAPHIC ADDRESS—BERNDYER, LONDON, E.C.3.
CABLEGRAMS—BERNDYER, LONDON.

Analytical Laboratory,
PEEK HOUSE,
20, EASTCHEAP,
LONDON, EC3M 1EL

12th September 1980

Result of Analysis 3935

Of a Sample of Labsure CRMX Nuts

Sent on Account of May & Baker Limited

Received on 2nd September 1980

Marked Batch No. SUD 93 Bag No. 327859 Study No. TA/80/160 1.9.80

Sealed Unsealed

		PARTS PER MILLION
Lead		0.93
Copper		16
Zinc		67
Cadmium	less than	0.2
Mercury		0.02
Arsenic	less than	0.1
Selenium		0.30
Aflatoxin B_1	less than	0.004
B_2 G_1 & G_2		not detected
Total DDT (DDE, DDT, TDE)	less than	0.01
Dieldrin	less than	0.01
Lindane	less than	0.01
Heptachlor	less than	0.01
Malathion	less than	0.01
Polychlorinated Biphenyls	less than	0.01

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

IOXYNIL TECHNICAL: Teratogenicity study by the oral route in the rat.

Appendix III

Analysis of weekly dosage form preparations.

Sample date	Analysis date	% nominal ioxynil found		
		5mg/kg	15mg/kg	35mg/kg
19/9/80	6/2/81	101.7	97.5	99.2
26/9/80	6/2/81	115.4	97.3	101.0
3/10/80	6/2/81	113.3	102.4	99.6
Mean % nominal compound found		110.1	99.1	99.9

IOXYNIL TECHNICAL :- Teratogenicity study by the oral route in the rat.
Appendix II

Dr. BERNARD DYER and PARTNERS (1948) Ltd.

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Analytical Laboratory,
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20, EASTCHEAP,
LONDON, EC3M 1EL

12th September 1980

Result of Analysis 3934

Of a Sample of Tap Water

Sent on Account of May and Baker Ltd.

Received on 2nd September 1980

Marked K5 D47 Building Study No. TA/80/160

Sealed Unsealed

		PARTS PER MILLION
Lead	less than	0.01
Copper	less than	0.01
Zinc		0.08
Cadmium	less than	0.01
Mercury	less than	0.01
Arsenic	less than	0.01
Selenium	less than	0.05
Aflatoxin B_1	less than	0.0001
B_2 G_1 & G_2		not detected
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.

EM/C3/25

Form AP 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 2 4 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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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 12591A

Triage of 8(e) Submissions

Date sent to triage: 12/14/95

NON-CAP (CAP)

Submission number: 12591A

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

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entire document: (0) 1 2 **pages** 1,2 **pages** 1,2, MB

Notes:

Contractor reviewer : PM **Date:** 4/16/95

CECATS/TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA:
Submission # 8EHQ- 1092 - 12591 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:
(0639) REFER TO CHEMICAL SCREENING
(0676) CAP NOTICE

VOLUNTARY ACTIONS:
0401 NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKER/USERS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP./USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

SUB. DATE: 09/14/92 OTS DATE: 10/07/92 CSRAD DATE: 02/09/95

CHEMICAL NAME: Benzonitrile, 4-hydroxy-3,5-diiodo- loxynil

CAS#: 1689-83-4 11

INFORMATION TYPE:		P F C	INFORMATION TYPE:		P F C	INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04	0216	EPI/CLIN	01 02 04	0241	IMMUNO (ANIMAL)	01 02 04
0202	ONCO (ANIMAL)	01 02 04	0217	HUMAN EXPOS (PROD CONTAM)	01 02 04	0242	IMMUNO (HUMAN)	01 02 04
0203	CELL. TRANS (IN VITRO)	01 02 04	0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04	(0243)	CHEM/PHYS PROP	01 02 04
0204	MUTA (IN VITRO)	01 02 04	0219	HUMAN EXPOS (MONITORING)	01 02 04	0244	CLASTO (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04	0220	ECO/AQUA TOX	01 02 04	0245	CLASTO (ANIMAL)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04	0221	ENV. OCCC/REL/FATE	01 02 04	0246	CLASTO (HUMAN)	01 02 04
(0207)	REPRO/TERATO (ANIMAL)	01 (02) 04	0222	EMER INCI OF ENV CONTAM	01 02 04	0247	DNA DAM/REPAIR	01 02 04
0208	NEURO (HUMAN)	01 02 04	0223	RESPONSE REQEST DELAY	01 02 04	(0248)	PROD/USE/PROC	01 02 04
0209	NEURO (ANIMAL)	01 02 04	(0224)	PROD/COMP/CHEM ID	01 02 04	0251	MSDS	01 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04	0225	REPORTING RATIONALE	01 02 04	0299	OTHER	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04	0226	CONFIDENTIAL	01 02 04			
0212	ACUTE TOX. (ANIMAL)	01 02 04	0227	ALLERG (HUMAN)	01 02 04			
0213	SUB ACUTE TOX (ANIMAL)	01 02 04	0228	ALLERG (ANIMAL)	01 02 04			
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04	0239	METAB/PHARMACO (ANIMAL)	01 02 04			
0215	CHRONIC TOX (ANIMAL)	01 02 04	0240	METAB/PHARMACO (HUMAN)	01 02 04			

TRIAGE DATA:	NON-CBI INVENTORY	ONGOING REVIEW	SPECIES	TOXICOLOGICAL CONCERN:	USE:	PRODUCTION:
	YES	YES (DROP/REFER)	RAT	LOW	R+D pesticide	import
CAS SR	NO	NO (CONTINUE)		(MED-High)		
	(IN HMINI)	REFER		HIGH		

COMMENTS

Developmental Tox Study:
by gavage 28 females per group
0, 5, 15, 35 mg/kg/day GD 5-17

Maternal Tox: At 35 mg/kg/day 6 deaths, ↓ body wt gains, ↓ food consumption. ↓ Body weight seen at 15 mg/kg/day (slight).

Fetal tox: Dose-related ↑ of supernumerary rib. ↓ mean fetal wt + minor anomalies at 35 mg/kg/day.