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PAGE 0 0/0

3M

February 20, 1981

8EHQ-0281-0373 Supplement
88-8100185

Document Control Officer
Chemical Information Division
Office of Toxic Substances (WH-557)
Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Gentlemen:

SUBJECT: 8EHQ-1180-0373C

This is in reference to the subject notice submitted November 19, 1980, wherein we indicated that, when available, a final written report of the teratology study would be provided. Accordingly, please find attached Report No. 1610 dated 2/18/81 and entitled: "Oral Teratology Study of in Rats."

In accordance with telephone instructions given us on February 18 by Ms. Jane Roemer of your office, we are also submitting a sanitized version of this letter and Report No. 1610 for the public file. As agreed in our conversation, no further substantiation or reference to omitted information is necessary with this letter since no new information is being claimed as confidential as described in our letter of February 10, 1981.

We trust that with the information provided herein, you will now be in a position to complete your review of the subject notice.

Sincerely,

Larry J. Magill

Larry J. Magill, Manager
Regulatory Affairs Department

ss

Enc.

c: Anthony Robbins, M.D.
Director, NIOSH
Park Lawn
5600 Fishers Lane
Rockville, MD 20855

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INFO. CONTROL BRANCH
1982 FEB 26 AM 8 31

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REPORT NO. 1610

DATE: 2/10/81

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Oral Teratology Study of in Rats

Experiment No.: 0580TR0010

Conducted At: Safety Evaluation Laboratory

St. Paul, Minnesota

Inclusive Dosing Period: August 19 to September 4, 1980

Study Director:

1-22-81
Date

1-22-81
Date

1/23/81
Date

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Summary

Oral administration of at 75, 37.5 and 25 mg/kg/day to pregnant Sprague-Dawley rats during days 6 through 15 of gestation (period of organogenesis) was teratogenic to rat fetuses. Teratogenic changes included a developmental eye abnormality, cleft palate, blood in the kidney parenchyma and sternebrae malformations. The developmental eye abnormality appeared to be an arrest in development of the primary lens fibers forming the embryonal lens nucleus followed by secondary aberrations of the secondary lens fibers of the fetal nucleus. The proportions of fetuses with the lens changes were significantly higher in all groups than in the control group. Cleft palates were produced in the 75 and 37.5 mg/kg/day groups. All three groups receiving compound had fetuses with blood in the kidney parenchyma. The sternebrae changes, although normally considered skeleton aberrations, were viewed as compound-related malformations because of their severity. also produced an increase in other fetal skeleton aberrations.

was not embryotoxic and did not affect the ovaries or reproductive tract contents of the dams.

was maternally toxic to the 75 and 37.5 mg/kg/day dose animals in reducing their group mean body weight gain during the dosing interval. Toxic clinical signs and deaths occurred in only the 75 mg/kg/day dose group.

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## Introduction

This teratology study [a] in rats was conducted to evaluate the embryotoxic and teratogenic effects of orally administered The study was sponsored by 3M Commercial Chemical Division, St. Paul, Minnesota and was conducted by the Safety Evaluation Laboratory, St. Paul, Minnesota. Two sets of compound administration groups were dosed between August 19 and September 4, 1980. The protocol and list of the principal participants and supervisory personnel can be found in Appendices I and II respectively.

All portions of this study were conducted according to the Good Laboratory Practice (GLP) regulations and the Safety Evaluation Laboratory Standard Operating Procedures (see Appendix III for Quality Assurance Unit statment). The storage location for specimens, raw data and a copy of the final report is maintained in the Safety Evaluation Laboratory's record archives.

## Methods

Time mated Sprague Dawley derived rats were obtained from Charles River Breeding Laboratory and assigned cages according to a computer-generated random numbers table. The rats were then divided into four groups of 22 animals weighing 140 to 240 grams. The rats were housed individually in hanging stainless steel cages with wire mesh floors and fronts in a temperature and humidity controlled room. Food [b] and water were available ad libitum. The lights were on a 12 hour light/dark cycle.

The animals were observed daily from day 3 through day 20 of gestation for abnormal clinical signs. Body weights were recorded on days 3, 6, 9, 12, 15 and 20 of gestation and the rats dosed accordingly using a constant dose volume of 5 ml/kg of body weight. The four groups were dosed with suspended daily in corn oil at 0, 75, 37.5 or 25 mg/kg/day. was administered daily by oral intubation with a syringe equipped with a ball-tipped intubation needle to the rats on days 6 through 15 gestation (day 0 indicated by sperm-positive vaginal smear). analytical characterization (see Appendix IV) was provided by 3M Commercial Chemical Division, St. Paul, Minnesota.

All surviving animals were sacrificed on day 20 by cervical dislocation and the ovaries and uterus, including its contents, were examined immediately to determine the following: number of corpora lutea, number of viable fetuses, number of resorption sites, pup weights and sex, and any gross fetal abnormalities. Approximately one-third of the fetuses were fixed in Bouin's solution for subsequent free-hand sectioning by the Wilson technique to determine visceral abnormalities. The remaining fetuses were preserved in alcohol for clearing and staining of the skeleton with alizarin red to detect skeletal abnormalities. Selected free-hand sections were processed for histological evaluation.

[a] Experiment No. 0680TT0010
[b] Purina Laboratory Chow, Ralston Purina Company, St. Louis, MO

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## Results and Discussion

was maternally toxic to the high and mid dose groups (75 and 37.5 mg/kg/day) in reducing their group mean body weight gain during the dosing interval. All groups had lower mean weight gain than the controls at all weighings during the dosing interval of days 6 through 15 of gestation (Table 1). In the case of the high dose group at gestation days 9, 12 and 15 and in the case of the mid dose group at gestation days 9 and 15, the group mean weight gains were significantly lower than the mean weight gains of the control group (0 mg/kg/day). The lower mean weight gains of the high and mid dose groups during the dosing interval were responsible for their significantly lower mean body weights between the end of dosing and the termination of the study (Appendix V). The mean body weights and mean weight gains of the low dose group (25 mg/kg/day) were not significantly different from the control.

Abnormal clinical signs were observed and deaths occurred only in the high dose group. Three rats in the high dose group died. One rat died without clinical signs. Two of the rats that died plus one surviving rat had abnormal compound-related clinical signs which included some of the following: thin, lethargic, ataxic, blood in stool, urinary incontinance and bloody nares. The onset of abnormal clinical signs was on day 11 but the signs disappeared in the surviving rat by day 19 of gestation. The remaining 18 high dose rats and the mid and low dose rats did not have abnormal compound-related clinical signs.

The compound was not embryotoxic and did not affect the ovaries or reproductive tract contents of the dams. The mean number of male, female, total and dead fetuses, the mean number of resorption sites, implantation sites and corpora lutea of the three dose groups were not significantly different from the control (Table 2, Appendix VI).

was not fetal toxic. However, the combination of reduced maternal body weight gain (Table 1) plus higher numbers of fetuses in the treatment groups than the control group (Table 2 Appendix VI) resulted in mean fetus weights of all groups which were significantly lower than the control mean fetus weight. The reduced mean fetus weights were not associated with an increase in runting or other gross fetus findings (Table 3).

administration resulted in malformations in fetal sternebrae. The changes, although normally considered skeleton aberrations, were interpreted as compound-related malformations because of their severity. The severity and often the incidence of sternebrae malformations were greater in the three treatment groups than the control group. These malformations included the following: sternebrae asymmetrical, sternebrae bipartite, sternebrae scrambled, sternebrae enlarged, sternebrae missing and sternebrae misshapen (Table 4). All three dose groups had significantly higher proportions of fetuses with sternebrae asymmetrical than the control group. In addition, the high dose group [illegible]

significantly higher proportion of fetuses with bipartite sternebrae than the control group.

An increase in other skeleton aberrations also occurred as the result of administration. These skeleton aberrations included nonossification changes of the cranial bones and sternebrae plus other sternebrae and rib changes (Table 4). The high dose group had significantly higher proportions of fetuses with all of these skeleton changes than the control group. The mid and low dose groups had significantly higher proportions of fetuses with some of these changes than the control group; notably nonossification of the cranial bones, sternebrae missing and 13 ribs spurred. The skeleton aberrations found are generally considered minor but they are of appreciable significance in this study with because of the high proportion of fetuses with the abnormalities.

The control group had a higher proportion of fetuses with one or two bodies of the vertebrae bipartite than the three treatment groups (Table 4). This difference was significant in all instances except for the finding of one body of the vertebrae bipartite in the low dose group.

administration produced the teratogenic effect of cleft palate in the high and mid dose groups and blood in the kidney parenchyma in all three dose groups. The proportions of fetuses with cleft palate and blood in the kidney parenchyma were sigificantly higher in the high dose group than in the control group (Table 5). No cleft palates were present in control and low dose fetuses examined.

was teratogenic to the eye of the rat at all dose levels administered in this study. The teratogenic effect was a developmental eye abnormality which appeared to be an arrest in development of the primary lens fibers forming the embryonal lens nucleus, followed by secondary aberrations of the secondary lens fibers of the fetal nucleus. All eye abnormalities were localized to the area of the embryonal lens nucleus although a variety of morphological appearances were present within that location. The range of morphological appearances as observed under the dissecting microscope varied from a slight discoloration running through the lens to a discoloration of part of the lens and the presence of a cleft beneath the lens epithelium (Table 5). Histologically the discolorations were due to the presence of lens vesicle remnants forming clefts or surrounding the lens nucleus. Also contributing to the discolorations were primary lens fibers which appeared to have not elongated and the possible presence of degenerated epithelial cells. Secondary lens fiber development progressed normally except immediately surrounding the abnormal embryonal nucleus. Prominant secondary aberrations of secondary lens fibers include V-shaped clefts between the embryonal nucleus and lens epithelium and lens vesicle remnants surrounding the nucleus.

The proportion of fetuses with the lens abnormality in one or both lenses was significantly higher in all groups than in the control group (Table 5).

No lens abnormalities occurred in the control group. A no-effect dose level for the teratogenic abnormality was not established in this study.

Further Discussion on Lens Embryology

Lens structural and functional requirements are met during embryonic development by the differentiation of highly specialized populations of cells from undifferentiated procursers and by the coordinated morphogenesis of the resulting tissues. Both processes are controlled to a remarkable extent by interactions which occur among developing tissues. Each tissue of the eye is brought to its final state of differentiation, its cell population, size and its definitive geometry, not only by intrinsic processes, but also by extrinsic influences exerted by neighboring tissues[1].

The embryonal origin of the lens is undifferentiated ectoderm. The tip of the optic vesicle, presumably the neural retina, plays the final role in inducing lens from overlying ectoderm and in aligning the lens precisely with the rest of the eye. Additional action of tissues derived from endoderm (foregut) and mesoderm (heart) on the same target tissue decreases the probability that lens formation would be aborted by accidents during the early phases of induction. While the nature of the inductive influence remains unknown, there are indications that substances may be transferred from the presumptive neural retina to the overlying ectoderm during induction. A prolonged period of inductive interaction not only increases the probability that lens induction will occur successfully in the face of interference, but provides a mechanism for continuously adjusting the size, shape, position and orientation of the lens to that of the retina[2].

During the early stages of the inductive process, the ectodermal cells immediately overlying the tip of the optic vesicle elongate perpendicularly to the body surface to form a thickened disc (lens placode). The change in cell shape is accomplished without change in cell volume. The number of cells, however, continues to increase during this period. Toward the end of lens placode formation, acidophilic fibrils appear in the apices of the lens placode cells. At about this time, the placode invaginates to form the lens cup. This invagination is independent of the concomitant invagination of the underlying optic vesicle, and is probably due to forces operating within the lens ectoderm. As the lens cup deepens, its opening (lens pore) becomes progressively constricted until its lips meet and fuse, cutting off the lens vesicle internally and re-establishing continuity in the overlying ectoderm. Closure of the lens pore is attended by, and possibly accomplished by, a local and temporary restricted wave of cell death. Following closure of the lens pore, the cells at the back of the lens vesicle continue to elongate, under the influence of the neural retina, to form the lens fibers. As the fibers grow the cavity of the lens vesicle is obliterated. The lens cells toward the ectoderm, which do not elongate further, form the lens epithelium[2].

The cuboidal lens epithelial cells which face the cornea continue to grow

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after the lens vesicle forms. As the cells rotate through the equator region, they take their places on the surface of the growing fiber mass. These cells differentiate into secondary lens fibers at the equator and elongate rapidly toward the poles of the lens where they meet with other fibers in planes of junction called sutures. As secondary fibers grow their nuclei become positioned at about the center of the fibers and form a convex lens bow outward. Since the newer fibers are always deposited superficially, the oldest fibers in the lens come to lie centrally and are referred to collectively as the lens nucleus. With time the lens cell nuclei in this region become pyenotic and finally disappear. The cell fibers, however, are not broken down and removed but remain in place. Thus the size and shape of the lens are controlled by factors which control the number, size and shape of the lens cells[2].

The teratogenic lens effect of probably occurred during the portion of organogenesis between differentiation of lens tissue from ectoderm and the formation of secondary lens fibers surrounding the embryonal lens nucleus. The exact time of the teratogenic insult and the morphogenesis of the abnormality were not determined in the study. The developmental lens abnormality appears to be unique because it has not been described as a compound-related abnormality[3]. A similar-appearing structural lens abnormality has been reported to occur spontaneously in rat fetuses but with a very low incidence of 1.2%[4]. The abnormality resembles the Fraser developmental lens abnormality of a mutant mouse strain which results from degenerative primary lens cells[5].

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Table 1

Oral Teratology Study of in Rats
Mean Body Weight Gains of Pregnant Rats Between Weighings
with Standard Deviations

| Dose Group | | Gestation Day 6 | 9 | 12 | 15 | 20 |
|---|---|---|---|---|---|---|
| 0 mg/kg/day | MEAN | 28 | 17 | 26 | 29 | 71 |
| | STAN. DEV | 5.5 | 7.5 | 5.8 | 4.9 | 12.1 |
| 75 mg/kg/day | MEAN | 30 | 0[a] | 6[a] | 2[a] | 69 |
| | STAN. DEV | 14.2 | 14.6 | 10.6 | 17.0 | 15.1 |
| 37.5 mg/kg/day | MEAN | 28 | 6[a] | 17 | 14[a] | 69 |
| | STAN. DEV | 5.4 | 10.9 | 9.8 | 10.4 | 15.8 |
| 25 mg/kg/day | MEAN | 27 | 11 | 20 | 22 | 73 |
| | STAN. DEV | 11.9 | 15.3 | 8.9 | 5.4 | 11.6 |

[a] Significantly lower than the control (Dunnett's t test $p < 0.05$)

Table 2

Oral Teratology Study of in Rats
Mean Litter Data with Fetus Weights and Standard Deviations

| Dose Group | No. of Animals | VIABLE FETUSES M | F | TOTAL | DEAD FETUSES | RESORPTION SITES | IMPLANTATION SITES | CORPORA LUTEA | MEAN WT. FETUS(G) |
|---|---|---|---|---|---|---|---|---|---|
| 0 mg/kg/day | 18 | 3.6 | 5.4 | 8.9 | 0.0 | 0.7 | 9.6 | 9.9 | 4.4 |
| | | 1.6 | 1.8 | 2.6 | 0.0 | 1.0 | 2.5 | 2.1 | 0.5 |
| 75 mg/kg/day | 17 | 5.1 | 4.7 | 9.8 | 0.1 | 0.5 | 10.4 | 10.5 | 3.7[a] |
| | | 2.1 | 2.3 | 2.1 | 0.2 | 0.6 | 1.9 | 2.2 | 0.5 |
| 37.5 mg/kg/day | 20 | 4.4 | 5.4 | 9.7 | 0.0 | 0.7 | 10.4 | 10.5 | 4.0[a] |
| | | 2.1 | 2.1 | 1.9 | 0.0 | 0.9 | 1.6 | 1.7 | 0.3 |
| 25 mg/kg/day | 21 | 4.3 | 5.8 | 10.1 | 0.0 | 0.5 | 10.7 | 11.3 | 4.0[a] |
| | | 1.6 | 1.9 | 1.9 | 0.0 | 0.5 | 2.0 | 1.9 | 0.3 |

[a] Significantly lower than the control (Dunnett's t test $p < 0.05$)

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Table 3

Oral Teratology Study of in Rats
Number of Fetuses with Gross Findings[a]

| Finding | 0 mg/kg/day | 75 mg/kg/day | 37.5 mg/kg/day | 25 mg/kg/day |
|---|---|---|---|---|
| Total Fetuses Examined | 161 | 167 | 195 | 213 |
| Runted | --- | 2 | --- | 2 |
| Umbilical hernia | 1 | --- | --- | 2 |
| Total Normal Fetuses | 160 | 165 | 195 | 209 |
| Total Abnormal Fetuses | 1 | 2 | 0 | 4 |

[a] Treatment groups were not significantly different from control (Chi-square $p < 0.05$)

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Table 4

Oral Teratology Study of in Rats
Number and Percent of Fetuses with Skeleton Findings

| Skeleton Finding | 0 mg/kg/day | | 75 mg/kg/day | | 37.5 mg/kg/day | | 25 mg/kg/day | |
|---|---|---|---|---|---|---|---|---|
| Fontanelle not closed | 27 | (24) | 26 | (22) | 25 | (18) | 28 | (19) |
| Holes in parietal | 1 | (1) | 1 | (1) | | | | |
| Parietal scalloped | 1 | (1) | | | | | | |
| Frontal nonossified | 21 | (19) | 62 | (53)[a] | 70 | (51)[a] | 75 | (50)[a] |
| Parietal nonossified | 21 | (19) | 62 | (53)[a] | 70 | (51)[a] | 74 | (50)[a] |
| Interparietal nonossified | 14 | (12) | 54 | (47)[a] | 46 | (33)[a] | 59 | (40)[a] |
| Occipital nonossified | | | 1 | (1) | | | | |
| Sternebrae nonossified | 80 | (71) | 100 | (86)[a] | 102 | (74) | 111 | (75) |
| Sternebrae asymmetrical | 10 | (9) | 42 | (36)[a] | 34 | (25)[a] | 36 | (24)[a] |
| Sternebrae bipartite | 2 | (2) | 37 | (32)[a] | 6 | (4) | 5 | (3) |
| Sternebrae scrambled | | | 1 | (1) | 1 | (1) | | |
| Sternebrae enlarged | | | 1 | (1) | | | | |
| Sternebrae misshapen | | | | | 1 | (1) | | |
| One sternebrae missing | 23 | (20) | 32 | (28) | 31 | (22) | 33 | (22) |
| Two sternebrae missing | 2 | (2) | 16 | (14)[a] | 9 | (7) | 16 | (11)[a] |
| Three sternebrae missing | | | 1 | (1) | | | | |
| One body vertebrae missing | | | 1 | (1) | | | | |
| 13 ribs | 1 | (1) | 3 | (3) | 3 | (2) | 5 | (3) |
| 13 ribs spurred | 3 | (3) | 32 | (28)[a] | 28 | (20)[a] | 9 | (6) |
| Wavy ribs | 5 | (4) | 8 | (7) | 4 | (3) | 2 | (1) |
| Protrusion on ribs | 8 | (7) | 12 | (10) | 5 | (4) | 7 | (5) |
| One body of the vertebrae bipartite | 29 | (26) | 15 | (13)[b] | 21 | (15)[b] | 30 | (20) |
| Two bodies of the vertebrae bipartite | 17 | (15) | 4 | (3)[b] | 5 | (4)[b] | 3 | (2)[b] |
| Three bodies of the vertebrae bipartite | | | | | 1 | (1) | 2 | (1) |
| Four bodies of the vertebrae bipartite | | | | | | | 1 | (1) |
| Five bodies of the vertebrae bipartite | | | | | | | 1 | (1) |
| Total Normal Fetuses | 9 | (8) | 2 | (2) | 6 | (4) | 7 | (5) |
| Total Abnormal Fetuses | 104 | (92) | 114 | (98) | 132 | (96) | 142 | (95) |
| Total Fetuses Examined | 113 | | 116 | | 138 | | 149 | |

[a] Significantly higher than the control (Chi-square $p < 0.05$)
[b] Significantly lower than the control (Chi-square $p < 0.05$)
( ) = percent of total examined



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Table 5

Oral Teratology Study of in Rats
Number and Percent of Fetuses with Internal Findings

| Internal Finding | 0 mg/kg/day | | 75 mg/kg/day | | 37.5 mg/kg/day | | 25 mg/kg/day | |
|---|---|---|---|---|---|---|---|---|
| Fetuses with eye abnormalities | 0 | | 35 | (69)[a] | 29 | (51)[a] | 27 | (42)[a] |
| Discoloration running through the lens of one eye | | | 7 | (13) | 2 | (4) | 1 | (2) |
| Discoloration running through the lens of both eyes | | | | | | | 1 | (2) |
| Discoloration running 1/2 to 3/4 through the lens of one eye | | | 16 | (31)[a] | 13 | (23)[a] | 10 | (16)[a] |
| Discoloration running 1/2 to 3/4 through the lens of both eyes | | | 5 | (10) | 1 | (2) | 5 | (8) |
| Discoloration in back of lens | | | | | | | 2 | (3) |
| Bubble on outside of lens and discoloration running through the lens of one eye | | | 1 | (2) | | | | |
| Cleft in the lens and discoloration running through the lens of one eye | | | 5 | (10) | 7 | (12)[a] | 4 | (6) |
| Cleft in the lens and discoloration running through the lens of both eyes | | | | | 1 | (2) | | |
| Bubble on outside of lens cleft in the lens of one eye | | | | | 1 | (2) | 1 | (2) |
| Cleft in the lens of one eye | | | 1 | (2) | 5 | (9) | 3 | (5) |
| Open space in the rear of the lens of one eye | | | | | | | 1 | (2) |
| Small eyes | | | 1 | (2) | | | | |
| Cleft palate | | | 7 | (14)[a] | 3 | (5) | | |
| Enlarged atriums | | | | | | | 2 | (3) |
| Enlarged renal pelvis area in the kidney | 5 | (10) | 1 | (2) | | | | |
| Blood in the kidney parenchyma | | | 11 | (22)[a] | 3 | (5) | 3 | (5) |
| Abdominal cavity full of blood | 1 | (2) | 3 | (6) | | | 1 | (2) |
| Total Normal Fetuses | 42 | (87.5) | 8 | (16) | 25 | (44) | 32 | (50) |
| Total Abnormal Fetuses | 6 | (12.5) | 43 | (84) | 32 | (56) | 32 | (50) |
| Total Fetuses Examined | 48 | | 51 | | 57 | | 64 | |

[a] Significantly different from the control (Chi-square $p < 0.05$)

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Appendix I

Oral Teratology Study of in Rats
Protocol

Objective

A teratology study will be used to evaluate the embryotoxic and teratogenic effects of orally administered to pregnant rats during the period of organogenesis. The procedure complies with the general recommendations of the FDA issued in January, 1966 ("Guidelines for Reproduction Studies for Safety Evaluation of Drugs for Human Use"). The study will be conducted according to the 1978 Good Laboratory Practice regulations and Safety Evaluation Laboratory's Standard Operating Procedures.

Sponsor

3M Commercial Chemical Division, St. Paul, Minnesota.

Testing Facility

Safety Evaluation Laboratory, St. Paul, Minnesota.

Study Director

Start of Dosing

Mid August, 1980.

Test System

Eighty-eight sexually mature, time mated Sprague-Dawley derived female rats from Charles River Breeding Laboratory will be housed in hanging stainless steel cages with wire mesh floors and fronts in a temperature and humidity controlled room. This strain of rats will be used because of historical control data and time mated females are readily avilable. Purina Laboratory Chow and water will be available ad litibum. The lights will be on a 12 hour light/dark cycle.

Test System Identification

Each animal will be ear tagged and that number will be indicated on the outside of the cage.

Randomization

The animals will be assigned cages according to a computer-generated random numbers table.

Appendix I (Concluded)

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Control Article

Corn oil.

Test Article

Analytical Specifications

The test article, composition and purity will be determined by the Sponsor (3M Commercial Chemical group) prior to the start of the study and at the end of dosing.

Dosage Levels and Experiment Design

The test article will be suspended in corn oil daily. The test article suspension and control article will be administered by oral intubation to the rats on days 6 through 15 of gestation according to the following:

| Dose Group | Dose Level | Group Size |
|---|---|---|
| High | 75 mg/kg/day | 22 ♀ |
| Mid | 37.5 mg/kg/day | 22 ♀ |
| Low | 25 mg/kg/day | 22 ♀ |
| Control | 0 mg/kg/day | 22 ♀ |

The oral route of administration will be used because toxicity has been defined by this route in a rangefinder study. No dietary contaminants are known to interfere with the test article.

The animals will be observed daily from day 3 through day 20 of gestation for abnormal clinical signs. Body weights will be recorded on days 3, 6, 9, 12, 15 and 20 or pregnancy and the rats dosed accordingly using a constant dose volume of 5 ml/kg of body weight.

The females will be killed on day 20 and the ovaries, uterus and its contents will be examined to determine: number of corpora lutea, number of fetuses (live and dead), number of resorption sites, number of implantation sites, pup weight and gross abnormalities. Approximately one-third of the pups will be fixed in Bouin's solution for subsequent free-hand sectioning by the Wilson technique to determine any visceral abnormalities using a dissecting microscope. The remaining approximately two-thirds of the pups will be fixed in ethyl alcohol for subsequent skeletal examination after clearing and staining with alizarin red.

Data Analysis and Final Report

The proposed statistical methods to be used for analysis of the data are: Dunnett's t test for dam and pup weights, number of fetuses, number of resorption sites, number of implantation sites and number of corpora lutea; chi-square for percent abnormalities. The proposed date for the final report is 2-3 months after detailed pup examinations have been completed (approximately first quarter, 1981).

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Appendix II

Oral Teratology Study of in Rats
List of Principal Participating Personnel

| NAME | FUNCTION |
| --- | --- |

Appendix III

STATEMENT OF QUALITY ASSURANCE



PAGE 00 27

STUDY NUMBER: 0680TR0010

TITLE: Oral Teratology Study of in Rats

Audits and/or inspections were performed by the Quality Assurance Unit for the above titled study, and reported to the study director and to management as follows:

| Date Performed | Date Reported |
|---|---|
| 20 August 1980 | 21 August 1980 |
| 2 September 1980 | 4 September 1980 |
| 20 and 21 January 1981 | 22 January 1981 |
| 22 January 1981 | 22 Jonaury 1981 |

Laboratory Quality Assurance

January 22, 1981
Date

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Test and/or Control Article Characterization

for

_____

1. The identity strength, uniformity, composition, purity or other pertinent characterizations of the test and/or control substances have been determined and documented as of May 8, 1980.

2. The method of synthesis or origin of the test and control substances, including their amount and the method of bioassay (if applicable) is documented.

yes X no ____

3. The stability of the test and/or control substances have been determined or will be determined as of Completion of The Testing If Necessary

The above information and documentation are located in the sponsor's records.

Sponsor 5/21/80
Date

Appendix V

Oral Teratology Study of in Rats
Individual and Mean Body Weights of Rats
With Standard Deviations

| Dose Group and Rat No. | Study Day 3 | 6 | 9 | 12 | 15 | 20 |
|---|---|---|---|---|---|---|
| 0 MG/KG/DAY | | | | | | |
| NOR 14756 | 204 | 230 | 248 | 276 | 304 | 380 |
| NOR 14757 | 196 | 234 | 242 | 278 | 304 | 377 |
| NOR 14760 | 213 | 250 | 257 | 286 | 310 | 359 |
| NOR 14776 | 184 | 209 | 222 | 243 | 278 | 339 |
| NOR 14777 | 232 | 262 | 274 | 307 | 341 | 426 |
| NOR 14778 | 186 | 219 | 232 | 264 | 297 | 377 |
| NOR 14780 | 226 | 255 | 271 | 300 | 325 | 396 |
| NOR 14796 | 190 | 220 | 232 | 254 | 280 | 347 |
| NOR 15385 | 197 | 231 | 251 | 271 | 301 | 384 |
| NOR 15387 | 188 | 216 | 238 | 264 | 292 | 376 |
| NOR 15388 | 196 | 228 | 254 | 286 | 322 | 406 |
| NOR 15389 | 193 | 222 | 242 | 269 | 293 | 346 |
| NOR 15405 | 184 | 209 | 219 | 235 | 260 | 310 |
| NOR 15406 | 195 | 220 | 240 | 261 | 299 | 373 |
| NOR 15407 | 238 | 267 | 272 | 287 | 312 | 390 |
| NOR 15408 | 239 | 258 | 278 | 306 | 331 | 401 |
| NOR 15409 | 193 | 216 | 240 | 263 | 297 | 379 |
| NOR 15425 | 154 | 171 | 206 | 232 | 255 | 313 |
| MEAN | 200 | 229 | 245 | 271 | 300 | 371 |
| STAN. DEV | 21.8 | 23.4 | 20.0 | 22.1 | 22.6 | 30.7 |
| NON PREGNANT ANIMALS | | | | | | |
| NOR 14758 | 212 | 244 | 259 | 273 | 268 | 293 |
| NOR 14759 | 213 | 223 | 226 | 242 | 249 | 264 |
| NOR 14779 | 194 | 222 | 227 | 255 | 243 | 250 |
| NOR 15386 | 192 | 225 | 243 | 244 | 252 | 280 |

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Appendix V (Continued)

Oral Teratology Study of in Rats
Individual and Mean Body Weights of Rats
With Standard Deviations

| Dose Group and Rat No. | Study Day 3 | 6 | 9 | 12 | 15 | 20 |
|---|---|---|---|---|---|---|
| 75 MG/KG/DAY | | | | | | |
| 00R 14761 | 215 | 247 | 238 | 255 | 252 | 307 |
| 00R 14762 | 224 | 252 | 218 | 217 | 243 | 323 |
| 00R 14763 | 188 | 211 | 208 | 230 | 246 | 320 |
| 00R 14764 | 193 | 220 | 220 | 245 | 250 | 309 |
| 00R 14765 | 220 | 260 | 267 | 292 | 303 | 384 |
| 00R 14782 | 202 | 233 | 209 | 204 | 210 | 267 |
| 00R 14783 | 207 | 245 | 237 | 264 | 262 | 317 |
| 00R 14785 | 208 | 246 | 249 | 281 | 282 | 370 |
| 00R 14797 | 188 | 214 | 210 | 237 | 225 | 291 |
| 00R 15390 | 176 | 209 | 222 | 226 | 186 | 231 |
| 00R 15391 | 204 | 238 | 228 | 191 | 168 | 0[a] |
| 00R 15392 | 212 | 225 | 233 | 232 | 225 | 285 |
| 00R 15393 | 234 | 252 | 251 | 263 | 265 | 311 |
| 00R 15394 | 194 | 222 | 227 | 237 | 240 | 309 |
| 00R 15410 | 185 | 211 | 215 | 183 | 182 | 260 |
| 00R 15411 | 140 | 221 | 231 | 216 | 237 | 313 |
| 00R 15414 | 219 | 240 | 261 | 255 | 259 | 351 |
| 00R 15426 | 195 | 216 | 243 | 243 | 276 | 368 |
| MEAN | 201 | 231 | 232 | 237[b] | 240[b] | 313[b] |
| STAN. DEV | 22.1 | 16.6 | 17.6 | 28.8 | 35.7 | 40.2 |
| NON PREGNANT ANIMALS | | | | | | |
| 00R 14781 | 208 | 243 | 208 | 165 | 0 | 0[a] |
| 00R 14784 | 195 | 221 | 194 | 177 | 204 | 239 |
| 00R 15412 | 224 | 245 | 229 | 179 | 149 | 0[a] |
| 00R 15413 | 223 | 241 | 248 | 240 | 242 | 258 |

[a] Rat died
[b] Significantly lower than the control (Dunnett's t test $p < 0.05$)

Appendix V (Continued)

Oral Teratology Study of in Rats
Individual and Mean Body Weights of Rats
With Standard Deviations

| Dose Group and Rat No. | Study Day 3 | 6 | 9 | 12 | 15 | 20 |
|---|---|---|---|---|---|---|
| 37.5 MG/KG/D | | | | | | |
| P0R 14766 | 183 | 214 | 216 | 237 | 254 | 301 |
| P0R 14767 | 209 | 250 | 240 | 269 | 261 | 335 |
| P0R 14768 | 208 | 234 | 238 | 264 | 287 | 368 |
| P0R 14769 | 218 | 245 | 249 | 273 | 294 | 362 |
| P0R 14770 | 212 | 242 | 251 | 280 | 299 | 377 |
| P0R 14787 | 187 | 215 | 223 | 250 | 267 | 339 |
| P0R 14788 | 176 | 204 | 209 | 226 | 245 | 305 |
| P0R 14789 | 197 | 222 | 212 | 234 | 246 | 303 |
| P0R 14790 | 192 | 221 | 225 | 251 | 278 | 336 |
| P0F 14798 | 196 | 228 | 210 | 236 | 238 | 303 |
| P0R 15395 | 182 | 204 | 227 | 240 | 262 | 332 |
| P0R 15396 | 191 | 212 | 233 | 235 | 243 | 316 |
| P0R 15397 | 217 | 245 | 266 | 282 | 307 | 382 |
| P0R 15398 | 231 | 249 | 256 | 269 | 279 | 360 |
| P0R 15399 | 189 | 217 | 225 | 237 | 245 | 303 |
| P0R 15415 | 205 | 239 | 246 | 269 | 292 | 374 |
| P0R 15416 | 210 | 243 | 254 | 270 | 295 | 371 |
| P0R 15417 | 222 | 244 | 245 | 257 | 262 | 340 |
| P0R 15418 | 196 | 231 | 252 | 267 | 287 | 355 |
| P0R 15419 | 240 | 263 | 257 | 246 | 237 | 340 |
| P0R 15427 | 192 | 216 | 231 | 238 | 245 | 268 |
| MEAN | 203 | 230 | 237 | 254[b] | 268[b] | 337[b] |
| STAN. DEV | 16.8 | 16.7 | 16.9 | 17.3 | 22.7 | 31.3 |
| NON PREGNANT ANIMALS | | | | | | |
| P0R 14786 | 188 | 206 | 213 | 214 | 222 | 226 |

[b] Significantly lower than the control (Dunnett's t test $p < 0.05$)

Appendix V (Concluded)

Oral Teratology Study of in Rats
Individual and Mean Body Weights of Rats
With Standard Deviations[g]

| Dose Group and Rat No. | Study Day -3 | 6 | 9 | 12 | 15 | 20 |
|---|---|---|---|---|---|---|
| 25 MG/KG/DAY | | | | | | |
| Q0R 14771 | 232 | 261 | 265 | 282 | 295 | 376 |
| Q0R 14772 | 212 | 240 | 247 | 263 | 273 | 347 |
| Q0R 14773 | 192 | 223 | 228 | 251 | 270 | 322 |
| Q0P 14774 | 182 | 210 | 215 | 236 | 256 | 326 |
| Q0R 14775 | 202 | 238 | 241 | 269 | 289 | 344 |
| Q0R 14791 | 217 | 251 | 263 | 291 | 315 | 389 |
| Q0R 14792 | 201 | 229 | 242 | 270 | 293 | 373 |
| Q0R 14793 | 221 | 254 | 251 | 281 | 300 | 375 |
| Q0R 14794 | 216 | 248 | 264 | 291 | 311 | 376 |
| Q0R 14795 | 193 | 223 | 223 | 250 | 276 | 345 |
| Q0R 14799 | 187 | 212 | 207 | 236 | 255 | 340 |
| Q0R 15400 | 153 | 131 | 201 | 214 | 242 | 317 |
| Q0R 15401 | 191 | 217 | 233 | 245 | 269 | 346 |
| Q0R 15402 | 206 | 238 | 255 | 269 | 297 | 394 |
| Q0R 15403 | 179 | 212 | 220 | 228 | 247 | 311 |
| Q0R 15404 | 192 | 229 | 254 | 274 | 308 | 393 |
| Q0R 15420 | 214 | 241 | 250 | 262 | 291 | 367 |
| Q0R 15421 | 183 | 207 | 219 | 234 | 255 | 364 |
| Q0R 15422 | 185 | 216 | 231 | 260 | 280 | 361 |
| Q0R 15423 | 228 | 253 | 262 | 257 | 282 | 365 |
| Q0R 15424 | 227 | 237 | 259 | 280 | 302 | 376 |
| MEAN | 201 | 228 | 240 | 259 | 281 | 355 |
| STAN. DEV | 19.8 | 28.0 | 19.9 | 21.3 | 21.6 | 27.3 |
| NON PREGNANT ANIMALS | | | | | | |
| Q0R 15428 | 196 | 225 | 231 | 234 | 236 | 271 |

[g] Means not significantly different from control (Dunnett's t test $p < 0.05$)

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## Appendix VI

### Oral Teratology Study of in Rats
### Individual Litter Data With Mean Fetus Weights

| Dose Group and Rat No. | VIABLE FETUSES M | F | TOTAL | DEAD FETUSES | RESORPTION SITES | IMPLANTATION SITES | CORPRA LUTEA | MEAN FETUS WT(G) AVG | M | F |
|---|---|---|---|---|---|---|---|---|---|---|
| 0 mg/kg/day | | | | | | | | | | |
| NOR 15385 | 4 | 7 | 11 | 0 | 0 | 11 | 7 | 3.3 | 3.3 | 3.4 |
| NOR 15386 | NOT PREGNANT | | | | | | | | | |
| NOR 15387 | 4 | 8 | 12 | 0 | 0 | 12 | 11 | 3.7 | 3.8 | 3.6 |
| NOR 15388 | 3 | 8 | 11 | 0 | 1 | 12 | 10 | 4.5 | 4.8 | 4.4 |
| NOR 15389 | 1 | 3 | 4 | 0 | 0 | 4 | 6 | 4.4 | 4.5 | 4.4 |
| NOR 15405 | 3 | 3 | 6 | 0 | 4 | 10 | 8 | 4.1 | 4.5 | 3.8 |
| NOR 15406 | 3 | 6 | 9 | 0 | 2 | 11 | 10 | 4.5 | 4.4 | 4.5 |
| NOR 15407 | 3 | 6 | 9 | 0 | 0 | 9 | 11 | 4.1 | 4.3 | 4.1 |
| NOR 15408 | 4 | 5 | 9 | 0 | 0 | 9 | 12 | 4.8 | 4.7 | 4.9 |
| NOR 15409 | 3 | 7 | 10 | 0 | 0 | 10 | 10 | 4.2 | 4.3 | 4.2 |
| NOR 15425 | 3 | 4 | 7 | 0 | 0 | 7 | 7 | 4.9 | 5.0 | 4.9 |
| NOR 14756 | 4 | 7 | 11 | 0 | 0 | 11 | 11 | 4.2 | 4.5 | 4.0 |
| NOR 14757 | 2 | 6 | 8 | 0 | 1 | 9 | 9 | 4.4 | 4.4 | 4.4 |
| NOR 14758 | NOT PREGNANT | | | | | | | | | |
| NOR 14759 | NOT PREGNANT | | | | | | | | | |
| NOR 14760 | 1 | 2 | 3 | 0 | 1 | 4 | 8 | 4.7 | 4.5 | 4.7 |
| NOR 14776 | 3 | 7 | 10 | 0 | 0 | 10 | 12 | 4.2 | 4.3 | 4.1 |
| NOR 14777 | 7 | 6 | 13 | 0 | 1 | 14 | 14 | 4.0 | 4.0 | 3.9 |
| NOR 14778 | 7 | 4 | 11 | 0 | 0 | 11 | 11 | 5.1 | 5.2 | 4.8 |
| NOR 14779 | NOT PREGNANT | | | | | | | | | |
| NOR 14780 | 4 | 4 | 8 | 0 | 1 | 9 | 11 | 5.5 | 5.7 | 5.3 |
| NOR 14796 | 5 | 4 | 9 | 0 | 1 | 10 | 11 | 3.9 | 3.8 | 3.9 |



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Appendix VI (Continued)

Oral Teratology Study of . . in Rats

Individual Litter Data With Mean Fetus Weights

| Dose Group and Rat No. | VIABLE FETUSES M | F | TOTAL | DEAD FETUSES | RESORPTION SITES | IMPLANTATION SITES | CORPORA LUTEA | MEAN FETUS WT(G) AVG | M | F |
|---|---|---|---|---|---|---|---|---|---|---|
| 75 mg/kg/day | | | | | | | | | | |
| 00R 15390 | 4 | 3 | 7 | 0 | 2 | 9 | 9 | 2.8 | 2.9 | 2.6 |
| 00R 15391 | DEAD | | | | | | | | | |
| 00R 15392 | 6 | 3 | 9 | 0 | 1 | 10 | 9 | 3.5 | 3.4 | 3.5 |
| 00R 15393 | 2 | 4 | 6 | 0 | 1 | 7 | 6 | 3.6 | 3.5 | 3.6 |
| 00R 15394 | 4 | 5 | 9 | 0 | 1 | 10 | 9 | 3.6 | 3.7 | 3.4 |
| 00R 15410 | 5 | 3 | 8 | 0 | 0 | 8 | 8 | 3.3 | 3.5 | 3.0 |
| 00R 15411 | 4 | 7 | 11 | 0 | 0 | 11 | 12 | 3.4 | 3.7 | 3.3 |
| 00R 15412 | DEAD | | | | | | | | | |
| 00R 15413 | NOT PREGNANT | | | | | | | | | |
| 00R 15414 | 2 | 11 | 13 | 1 | 0 | 14 | 14 | 4.1 | 3.9 | 4.1 |
| 00R 15426 | 5 | 7 | 12 | 0 | 0 | 12 | 12 | 4.2 | 4.4 | 4.1 |
| 00R 14761 | 8 | 2 | 10 | 0 | 0 | 10 | 12 | 3.4 | 3.4 | 3.3 |
| 00R 14762 | 8 | 4 | 12 | 0 | 0 | 12 | 11 | 3.3 | 3.3 | 3.3 |
| 00R 14763 | 8 | 2 | 10 | 0 | 1 | 11 | 11 | 3.7 | 3.8 | 3.1 |
| 00R 14764 | 5 | 4 | 9 | 0 | 0 | 9 | 9 | 3.6 | 3.5 | 3.6 |
| 00R 14765 | 7 | 4 | 11 | 0 | 1 | 12 | 13 | 4.1 | 4.1 | 4.1 |
| 00R 14781 | DEAD | | | | | | | | | |
| 00R 14782 | 6 | 5 | 11 | 0 | 0 | 11 | 11 | 3.3 | 3.5 | 3.1 |
| 00R 14783 | 1 | 5 | 6 | 0 | 1 | 7 | 8 | 4.7 | 5.3 | 4.6 |
| 00R 14784 | NOT PREGNANT | | | | | | | | | |
| 00R 14785 | 7 | 4 | 11 | 0 | 1 | 12 | 13 | 4.4 | 4.3 | 4.5 |
| 00R 14797 | 5 | 7 | 12 | 0 | 0 | 12 | 11 | 3.8 | 3.9 | 3.8 |



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Appendix VI (Continued)

Oral Teratology Study of in Rats

Individual Litter Data With Mean Fetus Weights

| Dose Group and Rat No. | VIABLE FETUSES M | F | TOTAL | DEAD FETUSES | RESORPTION SITES | IMPLANTATION SITES | CORPORA LUTEA | MEAN FETUS WT(G) AVG | M | F |
|---|---|---|---|---|---|---|---|---|---|---|
| **37.5 mg/kg/day** | | | | | | | | | | |
| POR 15395 | 4 | 5 | 9 | 0 | 0 | 9 | 9 | 3.7 | 3.9 | 3.5 |
| POR 15396 | 3 | 5 | 8 | 0 | 0 | 8 | 9 | 3.6 | 3.8 | 3.5 |
| POR 15397 | 5 | 6 | 11 | 0 | 0 | 11 | 10 | 4.3 | 4.5 | 4.2 |
| POR 15398 | 3 | 8 | 11 | 0 | 1 | 12 | 11 | 4.1 | 4.4 | 3.9 |
| POR 15399 | 3 | 5 | 8 | 0 | 2 | 10 | 8 | 4.0 | 4.3 | 3.8 |
| POR 15415 | 6 | 6 | 12 | 0 | 1 | 13 | 13 | 3.9 | 4.0 | 3.8 |
| POR 15416 | 9 | 3 | 12 | 0 | 0 | 12 | 11 | 3.8 | 3.8 | 3.8 |
| POR 15417 | 8 | 3 | 11 | 0 | 0 | 11 | 11 | 4.2 | 4.3 | 4.1 |
| POR 15418 | 2 | 8 | 10 | 0 | 1 | 11 | 12 | 4.7 | 5.0 | 4.6 |
| POR 15419 | 6 | 8 | 14 | 0 | 0 | 14 | 14 | 3.9 | 4.1 | 3.6 |
| POR 14766 | 5 | 3 | 8 | 0 | 3 | 11 | 13 | 3.7 | 3.8 | 3.5 |
| POR 14767 | 4 | 2 | 6 | 0 | 2 | 8 | 8 | 4.0 | 4.1 | 3.9 |
| POR 14768 | 3 | 8 | 11 | 0 | 0 | 11 | 11 | 3.8 | 3.9 | 3.7 |
| POR 14769 | 5 | 4 | 9 | 0 | 0 | 9 | 9 | 4.0 | 4.0 | 3.9 |
| POR 14770 | 5 | 4 | 9 | 0 | 1 | 10 | 10 | 4.1 | 4.3 | 3.9 |
| POR 14786 | NOT PREGNANT | | | | | | | | | |
| POR 14787 | 4 | 5 | 9 | 0 | 0 | 9 | 10 | 4.1 | 4.2 | 4.1 |
| POR 14788 | 4 | 7 | 11 | 0 | 1 | 12 | 12 | 4.4 | 4.3 | 4.4 |
| POR 14789 | 1 | 8 | 9 | 0 | 1 | 10 | 11 | 3.6 | 3.8 | 3.5 |
| POR 14790 | 1 | 7 | 8 | 0 | 1 | 9 | 11 | 4.4 | 4.1 | 4.5 |
| POR 14798 | 7 | 2 | 9 | 0 | 0 | 9 | 8 | 4.3 | 4.3 | 4.0 |

Appendix VI (Concluded)

Oral Teratology Study of in Rats

Individual Litter Data With Mean Fetus Weights

| Dose Group and Rat No. | VIABLE FETUSES M | F | TOTAL | DEAD FETUSES | RESORPTION SITES | IMPLANTATION SITES | CORPORA LUTEA | MEAN FETUS WT(G) AVG | M | F |
|---|---|---|---|---|---|---|---|---|---|---|
| 25 mg/kg/day | | | | | | | | | | |
| C0R 15400 | 6 | 4 | 10 | 0 | 1 | 11 | 9 | 3.3 | 3.5 | 3.2 |
| Q0R 15401 | 6 | 6 | 12 | 0 | 0 | 12 | 12 | 3.8 | 4.0 | 3.7 |
| Q0R 15402 | 3 | 8 | 11 | 0 | 0 | 11 | 11 | 4.3 | 4.4 | 4.3 |
| Q0R 15403 | 2 | 7 | 9 | 0 | 1 | 10 | 10 | 3.7 | 4.1 | 3.5 |
| Q0R 15404 | 5 | 7 | 12 | 0 | 1 | 13 | 14 | 4.5 | 4.6 | 4.4 |
| Q0R 15420 | 5 | 7 | 12 | 0 | 0 | 12 | 12 | 4.0 | 4.0 | 4.0 |
| Q0R 15421 | 3 | 6 | 9 | 0 | 0 | 9 | 9 | 3.6 | 3.8 | 3.5 |
| Q0R 15422 | 3 | 10 | 13 | 0 | 0 | 13 | 13 | 4.0 | 4.2 | 4.0 |
| Q0R 15423 | 5 | 6 | 11 | 0 | 1 | 12 | 11 | 4.0 | 4.0 | 3.9 |
| Q0R 15424 | 3 | 7 | 10 | 0 | 1 | 11 | 16 | 4.3 | 4.4 | 4.3 |
| Q0R 15428 | NOT PREGNANT | | | | | | | | | |
| Q0R 14771 | 5 | 6 | 11 | 0 | 1 | 12 | 13 | 4.1 | 4.3 | 4.0 |
| Q0R 14772 | 5 | 4 | 9 | 0 | 0 | 9 | 9 | 4.0 | 4.1 | 3.9 |
| Q0R 14773 | 2 | 3 | 5 | 0 | 0 | 5 | 10 | 3.8 | 3.8 | 3.8 |
| Q0R 14774 | 3 | 4 | 7 | 0 | 1 | 8 | 8 | 3.9 | 4.2 | 3.7 |
| Q0R 14775 | 6 | 3 | 9 | 0 | 1 | 10 | 12 | 3.9 | 3.8 | 4.2 |
| Q0R 14791 | 5 | 6 | 11 | 0 | 1 | 12 | 12 | 4.1 | 3.9 | 4.2 |
| Q0R 14792 | 3 | 8 | 11 | 0 | 0 | 11 | 12 | 3.7 | 3.5 | 3.7 |
| Q0R 14793 | 4 | 8 | 12 | 0 | 1 | 13 | 12 | 4.5 | 4.8 | 4.3 |
| Q0R 14794 | 3 | 5 | 8 | 0 | 0 | 8 | 10 | 3.9 | 4.0 | 3.9 |
| Q0R 14795 | 7 | 3 | 10 | 0 | 1 | 11 | 11 | 4.6 | 4.7 | 4.4 |
| Q0R 14799 | 7 | 4 | 11 | 0 | 0 | 11 | 12 | 4.5 | 4.5 | 4.5 |