

TSCA HEALTH & SAFETY STUDY COVER SHEET

MR 10328

TSCA CBI STATUS:

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1.0 SUBMISSION TYPE <i>Contains CBI</i> 8(d) <input type="checkbox"/> X 8(e) <input checked="" type="checkbox"/> <input type="checkbox"/> FYI <input type="checkbox"/> 4 <input type="checkbox"/> OTHER: Specify <u>8EHQ-0998-13922</u> - Intial Submission <input type="checkbox"/> -Follow-up Submission <input type="checkbox"/> X - Final Report Submission <input checked="" type="checkbox"/> Previous EPA Submission Number or Title if update or follow-up: _____ Docket Number, if any: # _____ Follow up to 8EHQ-97-13922 <u>PDC# 83970000172</u> <input type="checkbox"/> continuation sheet attached		
2.1 SUMMARY/ABSTRACT ATTACHED (may be required for 8(e): optional for §4, 8(d) & FYI) X - YES <input checked="" type="checkbox"/> NO <input type="checkbox"/>	2.2 SUBMITTER TRACKING NUMBER OR INTERNAL ID Cert# P 917006750 98-2-20	2.3 FOR EPA USE ONLY 99 SEP 23 AM 11:20 RECEIVED
3.0 CHEMICAL/TEST SUBSTANCE IDENTITY <i>-Contains CBI</i> <u>Reported Chemical Name (specify nomenclature if other than CAS name):</u> (Cyanamide, [3-(6-chloro-3-pyridinyl)methyl]-2]thiazolidinylidene]) CAS#: 111988-49-9 Purity _____% X - Single Ingredient <input checked="" type="checkbox"/> <input type="checkbox"/> Commerical/Tech Grade -Mixture <input type="checkbox"/> Trade Name: <u>YRC 2894</u> Common Name: <u>Chlornicotinyl</u>		
4.0 REPORT/STUDY TITLE <i>- Contains CBI</i> Further Examination of the Increased Occurrence of Dystocia & Stillbirths Observed in a Reproductive Bioassay with an Experimental Cyanamide 'YRC2894' <input type="checkbox"/> Continuation sheet attached		
5.1 STUDY/TSCATS INDEXING TERMS [CHECK ONE] HEALTH EFFECTS (HE): X ENVIRONMENTAL EFFECTS (EE): _____ ENVIRONMENTAL FATE (EF): _____		
5.2 STUDY/TSCATS INDEXING TERMS (see instructions for 4 digit codes) STUDY TYPE: _____ SUBJECT ORGANISM (HE, EE only): <u>RATS</u> ROUTE OF EXPOSURE (HE only): <u>Food</u> VEHICLE OF EXPOSURE (HEonly): <u>Oral</u> Other: <u>X</u> Other: _____ Other: _____ Other: _____		
6.0 REPORT/STUDY INFORMATION <input type="checkbox"/> Contains CBI <input type="checkbox"/> Study is GLP Laboratory <u>Bayer Toxicology, Stilwell, KS</u> Report/Study Date: <u>8/31/98</u> Source of Data/Study Sponsor (if different than submitter) _____ Number of pages <u>460</u> <input type="checkbox"/> continuation sheet attached		
7.0 SUBMITTER INFORMATION <input type="checkbox"/> Contains CBI Submitter: <u>Donald W. Lamb, Ph.D</u> Title: <u>V. P., Prod. Safety & Reg. Affrs</u> Phone: <u>412-777-7431</u> Company Name: <u>Bayer Corporation</u> Company Address: <u>100 Bayer Road</u> <u>Pittsburgh, PA 15205-9741</u> Submitter Address (if different): _____ Technical Contact: <u>Donald W. Lamb, Ph.D</u> Phone: <u>(412)777-7431</u> <input type="checkbox"/> continuation sheet attached		
8.0 ADDITIONAL/OPTIONAL STUDY COMMENTS <input type="checkbox"/> Contains CBI This compound is an experimental pesticide. <div style="text-align: center; font-size: 2em; font-weight: bold;">Contains No CBI</div> <input type="checkbox"/> continuation sheet attached		

BEHQ-97-13922



Submitter Signature: Donald W. Lamb Date: 9-16-98

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9.0 CONTINUATION SHEET

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98-2-20

CONTINUED FROM COVER SHEET SECTION # 2.1

Preliminary results of this study were submitted to EPA on April 29, 1997 (8EHQ-97-13922). It was suggested at that time that the test substance was promoting a trend toward an increase in estrogen and progesterone serum levels relative to control. Therefore this finalized report is be submitted to EPA under TSCA 8(e) as a follow-up.

DISCUSSION OF REPORTED EFFECTS: Both an increase in stillbirths as well as signs of dystocia (difficult labor) were noted during the 1st generation of a 2-generation reproductive bioassay with the test substance, a chemical agent with insecticidal properties. To develop data that could contribute to a mechanistic understanding of the test substance-induced alterations in the two reproductive endpoints, a modified 1-generation reproductive study was designed, which included a pre-mating phase, a gestation phase, and a post-partum phase. During these segments of the study, general toxicological endpoints as well as non-routine hormonal and histopathological assessments were made at 9 weeks pre-mating, gestation Days 18 and 21, and at 2 days post-partum.

Exposure was carried out via the diet at constant concentrations of either 0 or 800 ppm YRC 2894. As a focus for the study, it was hypothesized, insofar as dystocia has been associated with a hormonal imbalance in the rat, that a link may exist between chemical induction of metabolic activity in the liver and hormonal regulation of reproductive processes. Three specific areas of interest involved circulating levels of estrogen as well as the measurement of uterine and cervical levels of glutathione and prostaglandin.

A moderate decline in body weight gain was noted in the 800-ppm animals, during both the pre-mating and gestational phases of the study. Weight changes were not detected in any organ examined with the exception of the liver. In the liver, the test substance was found to induce a marked increase in both absolute and relative weight. In addition to weight changes, centrilobular hepatocytomegaly, microsomal enzyme induction, and proliferation of the smooth endoplasmic reticulum (SER) were also noted in the liver.

Though prostaglandin and reduced glutathione (GSH) measurements were unremarkable, elevations in circulating estradiol, progesterone, corticosterone, and luteinizing hormone were measured at either two or all three of the sampling phases of this study (pre-mating, gestation day 18 or 21, lactation day 2). However, despite the hormonal changes, estrogen and progesterone receptor populations in the cytosolic and nuclear fractions of the uterus remained unchanged.

All other hormones evaluated, which included thyroxine (T4), triiodothyronine (T3), thyrotropin (TSH), oxytocin, prolactin, and follicle stimulating hormone (FSH), were unaltered. These data suggest that the test substance is promoting, via its action at the liver, some form of interference with the capacity of the animals to regulate steroidal homeostasis. Further work on this project will focus on investigating more specific mechanisms of action indicative of a response secondary to a primary action on the liver.

Study Title

Further Examination of the Increased Occurrence of Dystocia
and Stillbirths Observed in a Reproductive Bioassay with an
Experimental Cyanamide (YRC 2894)



Data Requirement

Not Applicable

Author

W.R. Christenson

Study Completion Date

August 31, 1998

Sponsor

Bayer Corporation
Agriculture Division
Box 4913, Hawthorn Road
Kansas City, MO 64120-0013

Performing Laboratory

Bayer Corporation
Agriculture Division
Toxicology
17745 South Metcalf
Stilwell, KS 66085-9104

Laboratory Project Study ID

96-972-KF

STATEMENT OF DATA CONFIDENTIALITY

For this study, submitted and sponsored by the Bayer Corporation, no claim of confidentiality is made for any information contained within this report on the basis of its falling within the scope of Section 10(d)(1)(A), (B), or (C) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

Company Agent &
Vice President, Toxicology:

J.H. Thyssen


(Date)

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

Various tissue collected during this study were sent to Bayer AG in Germany, pending possible further analysis. No claims are made in this report regarding adherence to good laboratory practice as it may apply to any data that is forthcoming upon subsequent analysis of the transported tissue. Additionally, no claims are made in this report regarding adherence to good laboratory practice as it may apply to electron microscopy performed by the electron microscopy research laboratory, University of Kansas Medical Center. With these exceptions, this study, submitted and sponsored by the Bayer Corporation, was conducted in accordance with the Standards of Good Laboratory Practice (GLP) as described by the United States Environmental Protection Agency (EPA-FIFRA, 1989), Title 40 Code of Federal Regulations, Part 160 and The OECD Principles of Good Laboratory Practice, GD(92)32 (Paris, 1992).

Company Agent &
Vice President, Toxicology:

J.H. Thyssen

J.H. Thyssen 8-31-98
(Date)

Study Director:

W.R. Christenson

WR Christenson 8-31-98
(Date)

FLAGGING STATEMENT

I have applied the criteria of the Code of Federal Regulations, Title 40, Part 158.34 for flagging studies for potential adverse effects to the results of the attached study. This study, submitted and sponsored by the Bayer Corporation, neither meets or exceeds any of the criteria.

Company Agent &
Vice President, Toxicology:

J.H. Thyssen

J.H. Thyssen 8-31-98
(Date)

Study Director:

W.R. Christenson

W.R. Christenson 8-31-98
(Date)

PERSONNEL AND RESPONSIBILITIES

Company Agent & V.P., Toxicology:	J.H. Thyssen	<u>J.H. Thyssen</u>
Director, Toxicology Laboratory:	G.K. Sangha	<u>G.K. Sangha</u>
Director, Pathology Services:	B.P. Stuart	<u>B.P. Stuart</u>
Quality Assurance:	D.M. Wallace	<u>D.M. Wallace</u>
Diet Preparation:	R.E. Jones	<u>Ronald E. Jones</u>
Analytical Chemistry:	K.D. Moore	<u>K.D. Moore</u>
Animal Care:	R.E. Mueller	<u>R.E. Mueller</u>
Clinical Pathology:	A.M. Landes	<u>A.M. Landes</u>
Gross Pathology:	H.E. Hoss	<u>Herbert E. Hoss</u>
Histopathology:	K.L. Crabb	<u>K.L. Crabb</u>
Micropathology:	B.H. Hamilton	<u>B.H. Hamilton by B.P. Stuart</u>
Study Veterinarian:	H.D. Hoang	<u>H.D. Hoang</u>
Method Development:	P.D. Dass	<u>W.R. Christenson for P.D. Dass</u>
Study Conduct:	B.S. Wahle	<u>B.S. Wahle</u>
Study Conduct:	K.J. Freshwater	<u>K.J. Freshwater</u>
Study Direction & Author, General Report:	W.R. Christenson	<u>W.R. Christenson</u>

QUALITY ASSURANCE STATEMENT

Audit reports have been submitted to the study director and laboratory management documenting the status of compliance with applicable department standard operating procedures (SOPs), the study protocol, and GLP regulations. The quality assurance unit (QAU) monitored all phases of study conduct for this study and, at least annually, functions of all support areas for the study (Quality Assurance Audit Record, p. 394). In compliance with the standards of GLP, this final report for *laboratory project study ID No. 96-972-KF (study initiation 11-22-96; experimental start 11-25-96)* has been reviewed by the QAU. That review has confirmed that the methods and SOPs described herein as well as the results reported accurately reflect the raw data of the study.

Quality Assurance:

D. M. Wallace

Delma M. Wallace 8/31/98

NOTE TO READER

- 1) The data collection software utilized during this study was driven by a user-defined data collection protocol that was required (mandatory) before the actual process of collecting data could take place. Data tables may include the symbol "--," indicating an "outstanding" value if for any reason a scheduled measurement was missed. In most cases this results when an animal is removed from study (sacrificed *in extremis*, found dead, or sacrificed at term), preceding a scheduled measurement for that week.

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Further Examination of the Increased Occurrence of Dystocia
and Stillbirths Observed in a Reproductive Bioassay with an
Experimental Cyanamide (YRC 2894)

W.R. Christenson, B.S. Wahle, B.H. Hamilton, P.D. Dass,
A.B. Astroff, C. Crutch, B.P. Stuart, G.K. Sangha, and J.H. Thyssen

Bayer Corporation, Agriculture Division, Toxicology, 17745 South Metcalf,
Stilwell, KS 66085-9104

Abbreviated title: YRC 2894-induced changes in female rat reproductive parameters

Correspondence should be addressed to:

W. Russ Christenson, Ph.D.

Bayer Corporation

Toxicology

17745 South Metcalf

Stilwell, KS 66085-9104

Telephone: (913) 433-5225

Fax: (913) 433-5125

ABSTRACT

Further Examination of the Increased Occurrence of Dystocia and Stillbirths Observed in a Reproductive Bioassay with an Experimental Cyanamide (YRC 2894).

Both an increase in stillbirths as well as signs of dystocia (difficult labor) were noted during the 1st generation of a 2-generation reproductive bioassay with [3-[(6-chloro-3-pyridinyl)methyl]-2-thiazolidinylidene]-cyanamide (YRC 2894), a chemical agent with insecticidal properties. To develop data that could contribute to a mechanistic understanding of the YRC 2894-induced alterations in the two reproductive endpoints, a modified 1-generation reproductive study was designed, which included a pre-mating phase, a gestation phase, and a post-partum phase. During these segments of the study, general toxicological endpoints as well as non-routine hormonal and histopathological assessments were made at 9 weeks pre-mating, gestation Days 18 and 21, and at 2 days post-partum. Exposure was carried out via the diet at constant concentrations of either 0 or 800 ppm YRC 2894. As a focus for the study, it was hypothesized, insofar as dystocia has been associated with a hormonal imbalance in the rat, that a link may exist between chemical induction of metabolic activity in the liver and hormonal regulation of reproductive processes. Three specific areas of interest involved circulating levels of estrogen as well as the measurement of uterine and cervical levels of glutathione and prostaglandin. A moderate decline in body weight gain was noted in the 800-ppm animals, during both the pre-mating and gestational phases of the study. Weight changes were not detected in any organ examined with the exception of the liver. In the liver, YRC 2894 was found to induce a marked increase in both absolute and relative weight. In addition to weight changes, centrilobular hepatocytomegaly, microsomal enzyme induction, and proliferation of the smooth endoplasmic reticulum (SER) were also noted in the liver. Though prostaglandin and reduced glutathione (GSH) measurements were unremarkable, elevations in circulating estradiol, progesterone, corticosterone, and luteinizing hormone were measured at either two or all three of the sampling phases of this study (pre-mating, gestation day 18 or 21, lactation day 2). However, despite the hormonal changes, estrogen and progesterone receptor populations in the cytosolic and nuclear fractions of the uterus remained unchanged. All other hormones evaluated, which included thyroxine (T₄), triiodothyronine (T₃), thyrotropin (TSH), oxytocin, prolactin, and follicle stimulating hormone (FSH),

ABSTRACT (Contd.)

were unaltered. These data suggest that YRC 2894 is promoting, via its action at the liver, some form of interference with the capacity of the animals to regulate steroidal homeostasis. Further work on this project will focus on investigating more specific mechanisms of action indicative of a response secondary to a primary action on the liver.

INTRODUCTION

YRC 2894 is a chloronicotinyI agent (Fig. 1) with insecticidal properties that is currently undergoing regulatory testing to support registration as a agrochemical. Both an increase in stillbirths as well as signs of dystocia (difficult labor) were noted during the 1st generation of a 2-generation reproductive bioassay with the chemical (Eigenberg, 1997). Adverse changes in normal reproductive function are well documented in various species following exposure to pharmacologic/chemical agents. For example, inhibition of uterine contractions, delayed parturition, and prolonged labor have been observed in rats, rabbits, monkeys, and humans exposed to acetylsalicylic acid (aspirin) and indomethacin, both of which have also been shown to influence prostaglandin synthesis (Aiken, 1972; Chester et al., 1972; Hertelendy, 1973; Lewis and Schulman, 1973; Novy et al., 1974; Vane and Williams, 1973; Zuckerman et al., 1974). In addition, other effects on prostaglandin regulation, such as inhibition of prostaglandin E₂ (PGE₂) as well as stimulation of PGF₂ α and PGE₂ isomerase have been associated with the status of reduced glutathione (GSH) (Jouanen et al., 1985; Ogino et al., 1977), a nonprotein thiol which has also been linked to stimulation of prostaglandin synthesis in the rat uterus (Downing and Williams, 1980). Also in the rat uterus, GSH levels are believed to be regulated by a GSH peroxidase (Meister and Anderson, 1983), which is considered both an estrogen-dependent enzyme (Soujanen et al., 1980) and a modulator of prostaglandin synthase activity (Lands et al., 1971).

In applying these published and potentially reproductively-related observations to the findings noted in preliminary toxicity studies conducted with YRC 2894, the most striking effects noted in the rat were characterized by a profound ability to induce hepatic metabolizing capabilities (i.e. P-450 activity, glutathione transferase, UDP-glucuronosyl transferase, etc.) as well as to interfere with thyroidal economy in terms of both structure and function. Thus, the hormonal finding would appear consistent with a "secondary mechanism," identified with microsomal enzyme inducers such as phenobarbital and 3-methylcholanthrene, in which chemical stimulation of hepatic metabolism has been shown to "indirectly" influence the metabolism of thyroidal and estrogenic hormones (Suchar et al., 1996; Bastomsky, 1977; Gorski and Rozman, 1987; Lucier et al., 1975; McClain et al., 1989), and subsequently the structural and functional integrity of tissue responsive to these hormones. Therefore, based on the central role of prostaglandins in regulating delivery and their link, in terms of both synthesis and function, to estrogen and glutathione as described above,

INTRODUCTION (Contd.)

it was hypothesized that YRC 2894 may be mediating its reproductive toxicity through actions that are, at its core, the natural consequence of a chemically-induced enhancement of the metabolic status of the animal.

Moreover in the special case of the pregnant YRC 2894-exposed female rat, it was postulated that the nature or character of the metabolic response itself, under the confounding condition of pregnancy, leads to unique and interactive changes in glutathione and/or estrogenic homeostasis, which ultimately combine to compromise the capacity of the pregnant rat to adequately regulate uterine and/or cervical prostaglandin concentrations and deliver their pups unimpaired. To test the hypothesis, the following experimental aim was addressed: the hormonal, prostaglandin, and reduced glutathione profiles in the blood and/or uterine, ovarian, cervical, and hepatic tissue of the female rat following a pre- and post-conception exposure regimen to YRC 2894 was evaluated. The results of this experiment, which are described herein, provide no evidence of a YRC 2894-mediated interference with either glutathione and/or prostaglandin regulation. However, alterations in circulating levels of steroidal and gonadotropic hormones (estrogen, progesterone, corticosterone, and luteinizing hormone) coupled with hepatic changes indicative of microsomal enzyme induction (hepatocytomegaly, P450 induction, and proliferation of the SER) were noted.

MATERIALS AND METHODS

Chemicals. Technical grade YRC 2894 (batch No. 290894; CAS Registry No. 111988-49-9), a pale yellow powder, was obtained from Bayer AG of Leverkusen, Germany. The chemical was administered to the animals as a dietary admixture, based on its analytically determined percentage of purity. At all times prior to, during, and subsequent to the conclusion of the in-life portion of the study, the test batch of YRC 2894 was stored under freezer conditions. Both prior to and following the exposure segment of the study, the concentration/stability of YRC 2894 in the test batch, under storage conditions at the test facility, was determined by liquid chromatography to be at least 97% (Bayer AG, 1996). All other chemicals used were at least reagent grade and commonly available.

Animals. This study was conducted in accordance with published guidelines for the care and use of laboratory animals (National Research Council, 1996) and was approved by the Institutional Animal Care and Use Committee of the toxicology department of the Agriculture Division of Bayer Corporation. Rats were housed in a temperature-, humidity-, light-controlled, and AAALAC-accredited facility (room temperature 18 to 26°C, relative humidity 40 to 70%, daily photoperiod of 12 hr of fluorescent light [7:00 a.m. to 7:00 p.m.] alternating with 12 hr of darkness); deviations noted in these parameters were not of the frequency, magnitude, or duration to effect the status of the animals on study. Approximately four-week old male and female Sprague-Dawley rats were obtained from Sasco, Inc. (Kingston, NY); upon receipt, the animals were examined and subsequently euthanized (CO₂ asphyxiation) if deviations in general appearance and/or behavior were observed.

Those animals passing the initial shipment exam were individually-caged, throughout both the acclimation and pre-mating periods in suspended stainless steel wire-mesh cages, each containing a feeder, a source of water (pressure-activated water nipples), and deionized cage board in the bedding tray. During gestation and lactation, female animals were housed in polycarbonate shoebox-type enclosures containing Alpha-dri bedding. Observations for moribundity and mortality were performed at least once daily. Following one week of acclimation, male and female rats were assigned to either a control or a YRC 2894-exposure group using a weight stratification-based computer program obtained from INSTEM Computer Systems (Stone, Staffordshire, UK). Each animal on study was identified via an implanted microchip (Biomedic Data Systems, Inc., Maywood, NJ), encoded with a unique number specifying the animal's sex,

MATERIALS AND METHODS (Contd.)

dose group, cage number, and study affiliation. Food (Purina Mills Rodent Lab Chow 5001-4 in "etts" form, St. Louis, MO) and municipal tap water (dispensed by automatic watering system) were provided continuously for *ad libitum* consumption; food, as well as feeders and cages, were replaced/changed weekly. In addition, each animal's body weight and food consumption were monitored weekly with terminal body weights being taken just prior to killing for calculation of organ to body weight ratios.

Experimental design. All animals were 6-8 weeks of age when exposure to the chemical was initiated. The rats were administered YRC 2894 as a dietary admix for various times at constant target concentrations of either 0 (concurrent vehicle control) or 800 ppm. The design of this study called for groups of female rats to be sacrificed at one of three times, following continuous exposure to YRC 2894. Animals were killed following: (1) a 9 ± 1 week pre-mating phase; (2) a pre-mating + mating/pregnancy + gestation phase, concluding with sacrifice on Day 18 or Day 21 of gestation (Day 0 = sperm positive); and (3) a postpartum phase, concluding with sacrifice on post-delivery Day 2 (Day 0 = delivery). Estrous cyclicity was monitored by daily vaginal cytology; only rats that showed at least two consecutive 4-day estrous cycles were used in the study. All animals sacrificed at the 9 ± 1 week pre-mating phase of the study were monitored for 2 weeks to confirm normal cycling prior to being euthanized between the hours of 8:30 and 10:30 a.m. in the diestrus stage (Day 2) of their cycle.

Vaginal smears, lavages and timed pregnancies. Stages of estrus were determined from vaginal smears collected from female rats that were at least 7 weeks old. Smears were obtained by inserting (short of the cervix to avoid inducing pseudopregnancy) an eyedropper, containing a few drops of isotonic saline, into the rat's vagina. The contents of the eye dropper were then expelled into the vagina and subsequently aspirated back into the dropper. The aspirated saline was then placed on a compartmentalized slide and evaluated immediately using a light (phase contrast) microscope. Estrous cycle stages were identified by the type and abundance of cells in the vaginal smear. A smear composed predominantly of leukocyte cells suggested the rat was in the diestrus stage of their cycle; a smear composed principally of nucleated

MATERIALS AND METHODS (Contd.)

cells indicated the animal was in the proestrus stage of their cycle; while a smear composed of an increased proportion of cornified cells was considered indicative of the estrus phase of the rat's cycle. To initiate breeding, one to two females in late-proestrus to mid-estrus were housed with breeding males for up to 12 hr. With the exception of those females used for receptor analysis, control male animals were used to breed all female animals (control and treated) that were used for blood and tissue analyses. Breeding males and virgin females were approximately 17 weeks of age.

Diet preparation and analysis. An acetone/corn oil mixture was used as a vehicle to dissolve the YRC 2894 test material prior to mixing in the diet with a Hobart Model A200T or D300T mixer (Troy, OH). The control diet was prepared the same as the test diet, including the acetone/corn oil mixture and excluding only the test material. Replacement diet was prepared weekly and then stored under freezer conditions until presented to the animals the following week. The homogeneity, stability, and concentration of YRC 2894 in its dietary matrix were analytically verified using methodology described by Moore and Budzowski (1996). Briefly, homogeneity was confirmed by a comparative analysis of the concentration of 9 samples taken from 3 distinct sections (3 samples/section) of the mixing bowl; stability was confirmed for 7 and 28 days, following storage at room and freezer temperatures, respectively. The concentration of the principal/active ingredient (AI) of the test substance was analytically verified in the test diets at least 4 separate times during the in-life phase of this study (weeks 1, 7, 11, and 15). The mean analytical concentration of the treated test diet was 741 ppm, remaining within 8% of the corresponding nominal concentration of 800 ppm; the AI of the test substance was not detected in the control diet. In addition, one recovery sample was analyzed with each group of samples during the test concentration analyses. The recoveries ranged from 100 to 106% for rodent ration spiked with 800 ppm YRC 2894.

Collection of tissue and blood. At the time of sacrifice for the intervals indicated above (Plasma, for determination of circulating oxytocin levels, was collected on gestation Day 21; serum was collected at all other time points.), rats were asphyxiated in a CO₂ chamber and terminated by exsanguination (via cardiac puncture). For serum, blood was drawn using an untreated ice-chilled syringe/needle, transferred to serum separator tubes (Becton Dickinson VACUTAINER Systems, Rutherford, NJ) clotted, and the serum separated and frozen (-20°C) in 0.3 ml aliquots pending assay. The

MATERIALS AND METHODS (Contd.)

blood was allowed to clot at room temperature for at least 30 minutes prior to being centrifuged at 1,000-1,300 times gravity (g) for 10 ± 2 minutes at 4-10°C. For plasma, blood was drawn (6-8 ml) using an ice-chilled heparinized syringe/needle and transferred immediately into ice-chilled polypropylene tubes, containing 0.05 ml of an anticoagulant solution consisting of 7 mg KEDTA and 1.4 mg Aprotinin dissolved in a 0.9% saline solution. Following collection, a tube was inverted at least 10 times to ensure mixing with the anticoagulant and then stored on ice until undergoing centrifugation ($\sim 1,600g$) for 15 ± 2 minutes at 4-10°C. From the supernatant, 1.2 ml aliquots of plasma were transferred to polypropylene tubes and frozen at -20°C pending assay.

At each scheduled killing, liver, uterine, ovary, mammary, adrenal, pituitary, and cervical weights were determined. Tissue specimens were also collected for microscopic and/or biochemical analysis; hypothalamic tissue was collected but not weighed. All subsequent biochemical analyses were conducted on tissue that had been snap frozen in liquid nitrogen and stored at -80°C.

Clinical laboratory tests. Clinical chemistry parameters were assayed with a Hitachi 914 Analyzer (Boehringer Mannheim, Indianapolis, IN) and included sodium, potassium, chloride, urea nitrogen, glucose, creatinine, uric acid, triglyceride, cholesterol, creatine phosphokinase, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase, total bilirubin, total protein, albumin, inorganic phosphorus, calcium, and globulin.

Hepatic microsomal enzyme assays. In general, for all microsomal enzyme determinations, liver tissue was perfused with ice-cold saline, frozen in liquid nitrogen, and stored at -80°C pending assay. For cytochrome P450 and mixed function oxygenase determinations, microsomes were prepared as described by Parkinson and Safe (1979). Cytochrome P450 content was determined by the method of Omura and Sata (1964) from the carbon monoxide

MATERIALS AND METHODS (Contd.)

difference spectrum of dithionite-reduced microsomes based on an extinction coefficient of $91 \text{ mM}^{-1}\text{cm}^{-1}$. The activities of the mixed function oxygenases aminopyrine N-demethylase and p-nitroanisole O-demethylase were measured as described by Schoene *et al.* (1972) and Nettler and Seidel (1964), respectively.

Tissue prostaglandin and nonprotein sulfhydryl determinations. Uterine and cervical prostaglandin E_2 and F_2 alpha content were measured using enzyme-linked immunosorbent assay kits purchased from Neogen, Corp., Lexington, KY. The status of reduced glutathione (GSH) in the uterus and the liver was determined using a kit purchased from Calbiochem/Novabiochem Corp., La Jolla, CA.

Hormone determinations. Circulating follicle stimulating and luteinizing hormone concentrations were determined using radioimmunoassay immunoreagents, supplied by the Pituitary Hormone and Antisera Center, Harbor-UCLA Medical Center, Torrance, CA. All other blood hormone determinations were made using commercially available kits that were either used as sold, or, as in the case of the estrogen kit, modified slightly to improve the capacity of the kit to reliably measure more dilute blood concentrations of the steroid. The specific hormones measured and the minimum detectable concentration, respectively, for each procedure were as follows: total thyroxine (T_4), $0.50 \text{ } \mu\text{g/dl}$ (Diagnostic Products Corp., Los Angeles CA); total triiodothyronine (T_3), 0.2 ng/ml (Diagnostic Products Corp., Los Angeles CA); thyrotropin (TSH), 0.5 ng/ml (Amersham Life Science, Buckinghamshire, England); follicle stimulating hormone (FSH), 1.5 pg/ml ; luteinizing hormone (LH), 0.15 pg/ml ; estradiol (E_2), 0.8 pg/ml (Diagnostic Products Corp., Los Angeles, CA); progesterone, 0.1 ng/ml (Diagnostic Products Corp., Los Angeles, CA); corticosterone, 20 ng/ml (Diagnostic Products Corp., Los Angeles, CA); prolactin, 0.8 ng/ml (Diagnostic Products Corp., Los Angeles, CA); and oxytocin, 0.20 ng/ml (Peninsula Laboratories, Belmont, CA).

Receptor analyses. Dams were terminated as described and the uteri excised, weighed, and homogenized in ice-cold TEGMo buffer (10 mM Tris-HCl, 1.5 mM EDTA, 15 mM thioglycerol, 10 mM sodium molybdate, pH 7.4).

MATERIALS AND METHODS (Contd.)

The homogenates were then centrifuged at approximately 800g for 15 minutes at 0-4°C and separated into nuclear and cytosolic fractions. The nuclear fraction (pellet) was washed and resuspended with TEGMo buffer and the cytosolic fraction was centrifuged an additional 60 minutes at 105,000g, and the supernatant retained. All samples were frozen at -80°C. Prior to conducting the receptor binding studies the appropriate samples were thawed and diluted, if necessary, with TEGMo buffer to achieve a working concentration of approximately 1 mg/ml. Three hundred microliters of nuclear and/or cytosolic extracts were incubated at 25°C with 10 microliters radiolabeled receptor ligand (e.g., [³H]-Estradiol) in the absence or presence of 10 microliters unlabelled ligand (e.g., estradiol). Incubations were carried out in duplicate at room temperature. Prior to incubation a sample of the diluted extract was retained for analysis of actual protein concentration. Following incubation (30 minutes) the samples were washed three times with an ice-cold 20% Hydroxyapatite suspension in TEGMo buffer. Following the final wash, the pellet was resuspended in 70% ethanol and the radioactivity measured using liquid scintillation counting. Specific binding of the ligand to the receptor was determined by subtracting the non-specific binding from the total binding results. Receptor levels are reported as fmol/mg protein.

Histopathology. Adrenal, liver, uterine, ovarian, mammary, cervical, pituitary, and hypothalamic-related tissue were taken and preserved in EM grade formalin. Representative sections of the tissues collected were processed, embedded in paraffin, sectioned, mounted, and stained with hematoxylin and eosin for examination under the light microscope. A 5-level grading system (minimal, mild or slight, moderate, marked, and severe) was used to evaluate the organs histologically. Portions of some liver tissue were also preserved in universal fixative to allow for examination under the electron microscope.

Statistics. Data were analyzed for statistically significant differences by Student's t test (unpaired). All differences with p values ≤ 0.05 were defined as statistically significant and subsequently evaluated for their possible association to treatment. All statistical evaluations were performed using software from either INSTEM Computer Systems or Jandel Scientific (Corte Madera, CA).

RESULTS AND DISCUSSION

YRC 2894 Dietary Exposure Rates

For the experimental results described below, the mean daily intake of YRC 2894 was determined from feed consumption, body weight, and diet analysis data. A daily dose of 54.0 or 61.0 mg/kg body wt was calculated for male and female animals, respectively. The test substance was administered in the feed, which was available for ad libitum consumption, over approximately 10 weeks for males (pre-mating phase) and up to 14 weeks for females (pre-mating, gestation, lactation) at a nominal dietary concentration of 800 ppm.

Effect on YRC 2894 on Body Weight, Organ Weight and Clinical Observations

Individual terminal body weight data, including mean, standard error and statistical significance, are shown in Appendix I, Tables 53-56; individual absolute and organ/terminal body weight, including mean, standard error and statistical significance, are shown in Appendix I, Tables 57-96.

As shown in Appendix I, Figure 2, a moderate, yet statistically significant decline, in body weight gain, which was not attributable to alterations in food consumption, was noted in the 800-ppm animals, during both the pre-mating and gestational phases of the study. However, neither absolute or relative weight changes were measured in any organ examined with the exception of the liver. In the case of the liver, YRC 2894 was found to induce a marked increase in both absolute and relative weight (Appendix I, Tables 73-80). Other findings often associated with hepatocytomegaly included microsomal enzyme induction (Appendix I, Tables 169-177) and proliferation of the SER (Appendix I, Figure 3) both of which were also observed in this study.

Clinically, two treated females (ID Nos. KF1169 and KF1171) were observed that either did not start and/or did not complete the delivery process. In one case, several pups were successfully delivered before the process was halted. Four pups remained in the uterus at the time of necropsy; two were alive, two were dead. In the second case, the female showed only slight indications that parturition had been initiated and did not deliver. In both cases, the animals were

RESULTS AND DISCUSSION (Contd.)

given at least 24 hours to complete the process. Based on these characterizations, the possibility that the stillbirths and the dystocia-like response observed in the earlier study (Eigenberg, 1997) were reproduced in these two animals cannot be excluded. All other clinical findings noted during this study were considered unremarkable.

Effect of YRC 2894 on Tissue Prostaglandin and GSH Content.

Individual prostaglandin and GSH data, including mean, standard error and statistical significance are shown in Appendix I, Tables 1-16 and 45-52, respectively.

Absolute and relative changes in cervical and uterine prostaglandin E₂ and F₂alpha content remained unperturbed in YRC 2894-exposed cycling, pregnant (Day 18), and postpartum (lactation Day 2) animals. Similarly, alterations in GSH were not noted in either the liver or the uterus in samples analyzed from the same three phases of the study. These data suggest that the occurrence of dystocia and stillbirths, observed in an earlier reproductive bioassay with YRC 2894, are not due to either a direct or indirect action of YRC 2894 on prostaglandin and/or glutathione regulation.

Effect on YRC 2894 on Clinical and Microsomal Enzyme Endpoints

Individual data, including mean, standard error and statistical significance, are shown in Appendix I, Tables 97-177.

These endpoints were generally unremarkable with the exception of elevations in circulating cholesterol (Tables 154-156) and hepatic microsomal enzyme activity (Tables 169-177). As cholesterol is a key precursor in the process of steroidal hormone synthesis, these data continue to suggest a hepatic role in the altered hormone profile observed in this study and described below.

RESULTS AND DISCUSSION (Contd.)

Effect of YRC 2894 on Circulating Hormone Concentrations

Individual data, including mean, standard error and statistical significance, are shown in Appendix I, Tables 17-44.

Elevations in estrogen, progesterone, corticosterone, and luteinizing hormone were measured at either two or all three of the sampling phases of this study (pre-mating, gestation day 18 or 21, lactation day 2). All other hormones evaluated, which included T₄, T₃, TSH, oxytocin, prolactin, and FSH, remained unchanged. These data suggest a very broad dysregulation of steroidal hormone homeostasis is occurring as a result of exposure to YRC 2894. Two potential target sites where such a profile might be expected to emerge would be the hypothalamus and the pituitary. Histopathology of both tissues, however, showed no evidence of a chemically-mediated toxicity. In addition, microscopic examination of the ovary and the adrenal gland was also unremarkable. Only the liver as mentioned previously, which can represent a secondary and unregulated source of steroidal hormone (i.e. high dose chemical induction of P450-dependent enzymes involved in synthesis and metabolism such as CYP19 aromatase), showed signs of microscopic change, characterized by hepatocytomegaly and proliferation of the SER, in response to YRC 2894.

Effect of YRC 2894 on Uterine Estrogen and Progesterone Receptor Populations

Individual data, including mean, standard error and statistical significance, are shown in Appendix I, Tables 178-181.

Uterine estrogen and progesterone receptor concentrations were determined in both the nuclear and cytosolic cellular fractions. Both nuclear and cytosolic estrogen receptor concentrations were unaffected by YRC 2894 exposure. For example, cytosolic estrogen receptors ranged from 619 to 3140 fmol/mg protein in the control dams and from 548 to 3942 fmol/mg protein in the YRC 2894-exposed dams. Similar progesterone receptor concentrations were observed between control and YRC 2894-exposed dams (cytosolic and nuclear).

RESULTS AND DISCUSSION (Contd.)

Histopathological Assessment

With the exception of the liver, no evidence of a compound-related effect was observed in any other tissue examined. As mentioned above, liver changes in this study were characterized by a centrilobular hepatocytomegaly, which was associated with an increase in the SER, identified by electron microscopy. Moreover, elevations in ALT were not observed in the circulation and no evidence of bile (Hall's stain) or iron accumulation (Perl's Prussian blue stain) could be detected microscopically. Thus, the liver changes induced by YRC 2894 appear to be fundamentally adaptive in character.

Conclusion

In summary these data suggest that YRC 2894 is mediating its effects on circulating steroid and steroid-related hormones as a secondary response to some form of primary effect initiated at the liver. To elaborate on this postulate, subsequent work on this project will focus on the role that YRC 2894-mediated induction of hepatic CYP19 aromatase activity may be playing in the altered hormone profile that emerged in this study. Thus, a hepatically-driven interference with the capacity of some of the dams to effectively regulate their hormone profile, coupled with the stress of pregnancy, may represent the most likely explanation behind the observations of dystocia and stillbirths noted in the YRC 2894 reproductive bioassay.

ACKNOWLEDGMENTS

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FIGURE LEGENDS

FIG. 1. Chemical structure of YRC 2894.

FIG. 2. Effect of YRC 2894 on body weight and food consumption. Cycling female rats were dosed continuously with YRC 2894 for 8 ± 1 weeks; the animals were mated and exposure to the chemical continued through pregnancy and delivery, concluding at Day 2 of lactation (Day 0 = delivery). YRC 2894 was administered as an admix to the feed at a constant concentration of either 0 or 800 ppm; feed was available on a continuous basis for *ad libitum* consumption by the animals. ***Inset:*** Corresponding profile of food consumption over the same time period. An ***asterisk (*)*** indicates statistical significance relative to control by Student's t test (unpaired); $p \leq 0.05$.

FIG. 3. Electron micrograph of liver from pre-mating group fed 800 ppm YRC 2894, with areas of proliferation of the SER. x8000.

APPENDIX I

FIGURES AND TABLES

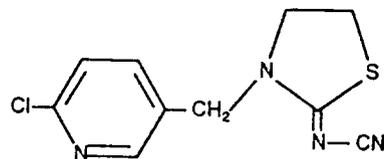


FIG. 1. Chemical structure of YRC 2894.

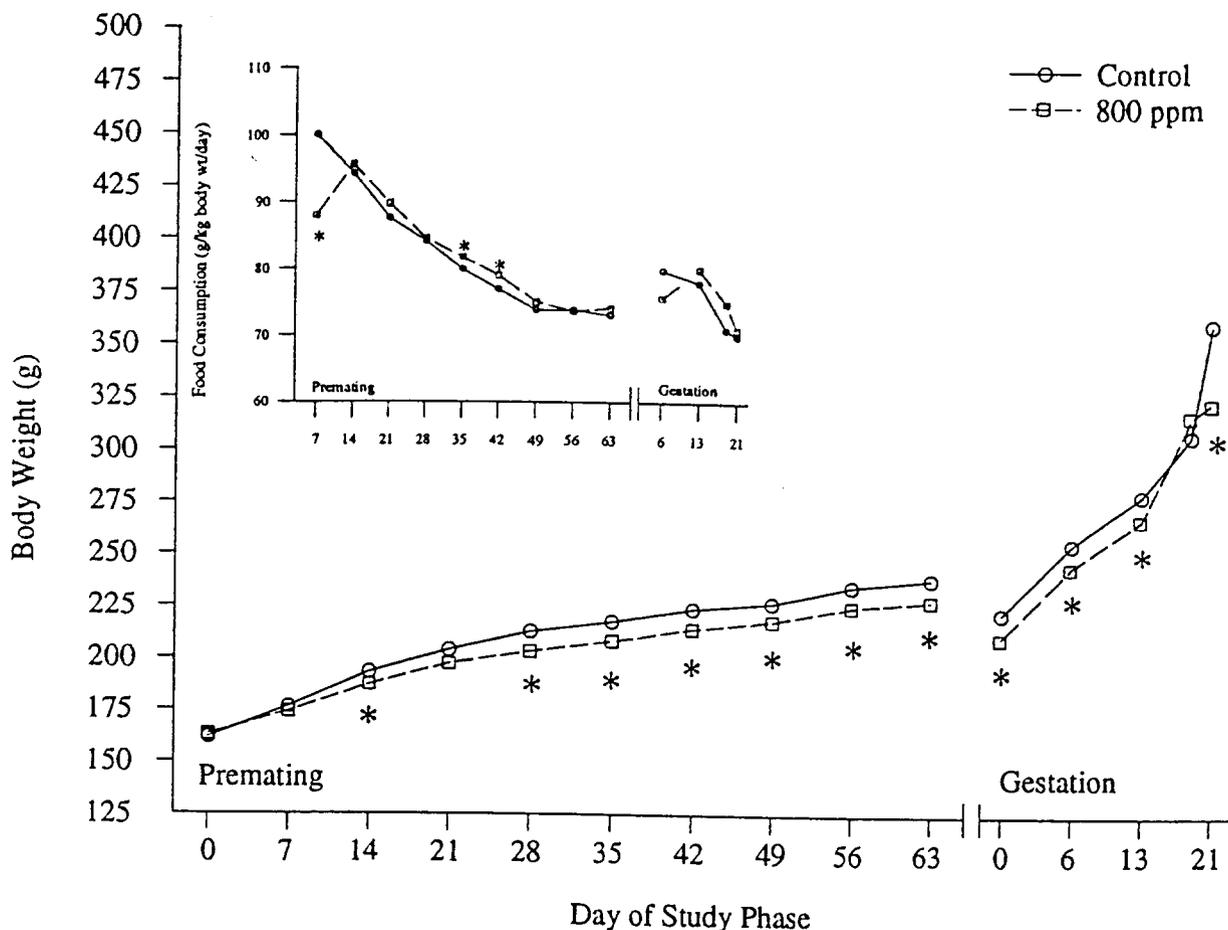


FIG. 2. Effect of YRC 2894 on body weight and food consumption. Cycling female rats were dosed continuously with YRC 2894 for 8 ± 1 weeks; the animals were mated and exposure to the chemical continued through pregnancy and delivery, concluding at Day 2 of lactation (Day 0 = delivery). YRC 2894 was administered as an admix to the feed at a constant concentration of either 0 or 800 ppm; feed was available on a continuous basis for *ad libitum* consumption by the animals. *Inset:* Corresponding profile of food consumption over the same time period. An asterisk (*) indicates statistical significance relative to control by Student's t test (unpaired); $p \leq 0.05$.

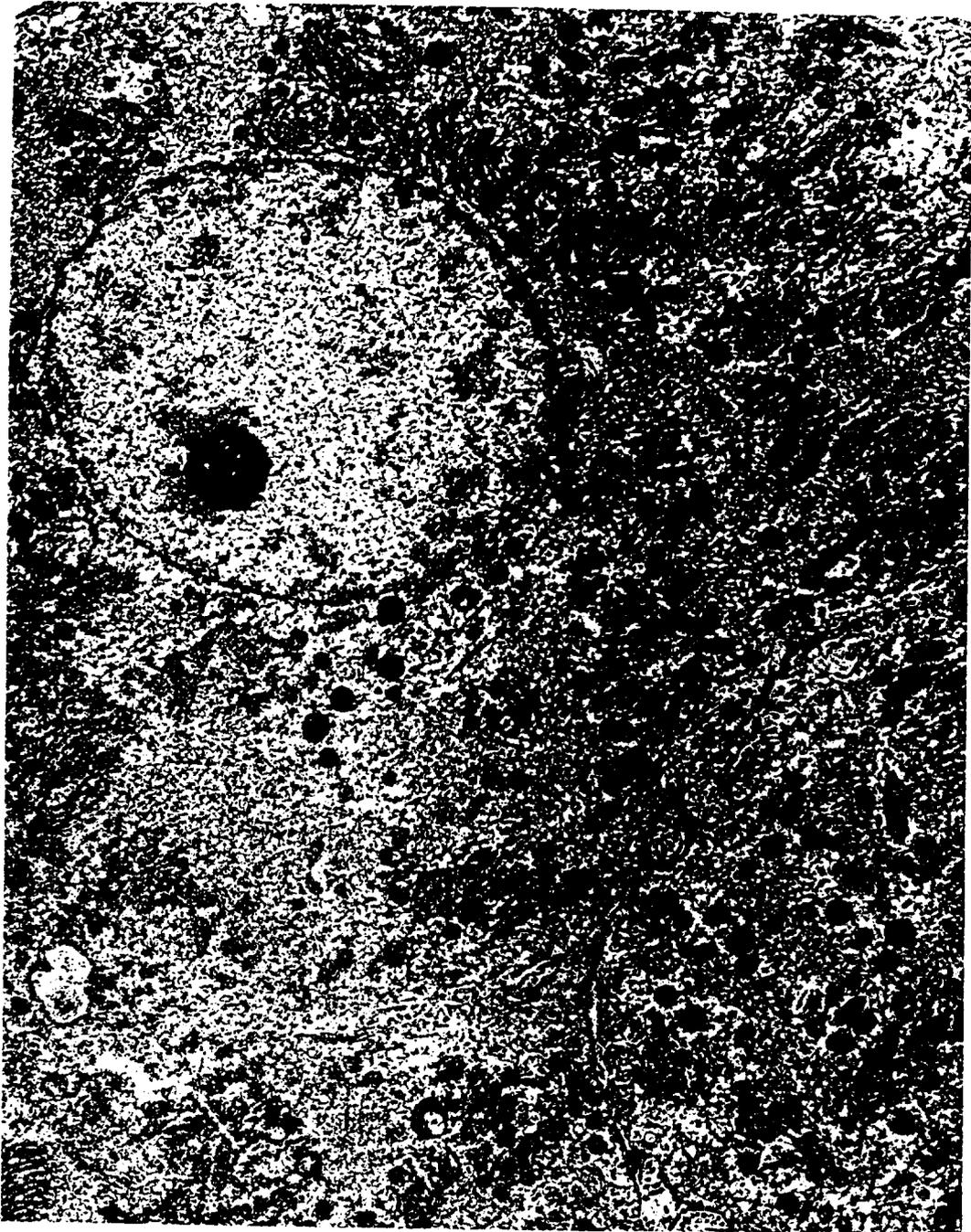


FIG. 3. Electron micrograph of liver from pre-mating group fed 800 ppm YRC 2894, with areas of proliferation of the SER. x8000.

TABLE 1

**Individual Data Depicting the Effect of YRC 2894
 on Cervical Prostaglandin E₂ (PG E₂) Content in Cycling Rats^a**

Dose (ppm)	Animal Number	PG E ₂ (ng/gm cervix)
0	KF0101	--- ^b
0	KF0107	115.5
0	KF0109	121.8
0	KF0113	63.7
0	KF0115	125.5
0	KF0118	---
0	KF0119	120.5
0	KF0120	98.9
0	KF0121	73.1
0	KF0122	---
0	KF0124	98.6
0	KF0126	70.6
0	KF0131	1509.0
0	KF0133	1306.0
0	KF0137	83.2
	MEAN	315.5
	SE	147.9

Table 1 continued on following page

TABLE 1

Individual Data Depicting the Effect of YRC 2894
 on Cervical Prostaglandin E₂ (PG E₂) Content in Cycling Rats^a

Dose (ppm)	Animal Number	PG E ₂ (ng/gm cervix)
800	KF1101	48.8
800	KF1102	46.2
800	KF1103	156.3
800	KF1106	--- ^b
800	KF1107	76.7
800	KF1110	---
800	KF1113	---
800	KF1115	43.2
800	KF1116	222.7
800	KF1120	218.8
800	KF1123	131.6
800	KF1126	149.0
800	KF1132	207.9
800	KF1136	333.7
800	KF1138	183.7
	MEAN	151.6
	SE	25.6

^a Cycling female rats were dosed with YRC 2894 for 8 ± 1 consecutive weeks. The YRC 2894 was administered to the animals as an admix to the diet at a constant concentration of either 0 or 800 ppm. During the study, feed was available on a continuous basis for *ad libitum* consumption by the animals.

^b "---" indicates insufficient sample for analysis

TABLE 2

Individual Data Depicting the Effect of YRC 2894
on Cervical Prostaglandin E₂ (PG E₂) Content in Pregnant Rats at Gestation Day 18^a

Dose (ppm)	Animal Number	PG E ₂ (ng/gm cervix)
0	KF0103	--- ^b
0	KF0104	---
0	KF0106	---
0	KF0108	35.1
0	KF0111	97.3
0	KF0116	23.9
0	KF0123	---
0	KF0123	29.6
0	KF0132	20.4
0	KF0142	22.7
0	KF0147	18.7
0	KF0181	25.3
0	KF0183	33.0
0	KF0184	27.1
	MEAN	33.3
	SE	7.3

Table 2 continued on following page

TABLE 2

Individual Data Depicting the Effect of YRC 2894
 on Cervical Prostaglandin E₂ (PG E₂) Content in Pregnant Rats at Gestation Day 18^a

Dose (ppm)	Animal Number	PG E ₂ (ng/gm cervix)
800	KF1108	--- ^b
800	KF1111	---
800	KF1114	35.7
800	KF1118	23.5
800	KF1127	---
800	KF1134	34.7
800	KF1135	30.3
800	KF1156	20.9
800	KF1159	37.6
800	KF1163	52.1
800	KF1165	42.6
	MEAN	34.7
	SE	3.6

^a Cycling female rats were dosed with YRC 2894 for 8±1 weeks; the animals were mated and exposure to the chemical continued up through Day 18 of gestation. The YRC 2894 was administered to the animals as an admix to the diet, which was available for *ad libitum* consumption, at a constant concentration of either 0 or 800 ppm.

^b "---" indicates insufficient sample for analysis

TABLE 3

**Individual Data Depicting the Effect of YRC 2894
 on Cervical Prostaglandin E₂ (PG E₂) Content in Pregnant Rats at Gestation Day 21^a**

Dose (ppm)	Animal Number	PG E ₂ (ng/gm cervix)
0	KF0110	--- ^b
0	KF0114	13.3
0	KF0134	8.1
0	KF0141	7.0
0	KF0143	6.4
0	KF0145	7.3
0	KF0146	4.6
0	KF0152	9.9
0	KF0153	7.9
0	KF0163	---
0	KF0165	---
0	KF0168	6.2
0	KF0169	16.2
0	KF0173	10.2
	MEAN	8.8
	SE	1.0

Table 3 continued on following page

TABLE 3

Individual Data Depicting the Effect of YRC 2894
on Cervical Prostaglandin E₂ (PG E₂) Content in Pregnant Rats at Gestation Day 21^a

Dose (ppm)	Animal Number	PG E ₂ (ng/gm cervix)
800	KF1112	9.2
800	KF1121	--- ^b
800	KF1122	---
800	KF1125	13.7
800	KF1128	---
800	KF1130	21.8
800	KF1137	8.2
800	KF1147	11.2
800	KF1162	5.6
800	KF1164	10.5
800	KF1167	6.7
800	KF1170	8.3
800	KF1175	6.2
800	KF1176	---
800	KF1179	---
800	KF1181	9.6
	MEAN	10.1
	SE	1.4

^a Cycling female rats were dosed with YRC 2894 for 8 ± 1 weeks; the animals were mated and exposure to the chemical continued up through Day 21 of gestation. The YRC 2894 was administered to the animals as an admix to the diet, which was available *ad libitum* consumption, at a constant concentration of either 0 or 800 ppm.

^b "---" indicates insufficient sample for analysis

TABLE 4

Individual Data Depicting the Effect of YRC 2894
 on Cervical Prostaglandin E₂ (PG E₂) Content in Female Rats on Lactation Day 2^a

Dose (ppm)	Animal Number	PG E ₂ (ng/gm cervix)
0	KF0105	6.2
0	KF0117	23.1
0	KF0136	2.1
0	KF0140	--- ^b
0	KF0148	9.5
0	KF0151	---
0	KF0156	---
0	KF0157	15.6
0	KF0160	19.4
0	KF0171	14.4
0	KF0174	7.3
0	KF0178	13.1
0	KF0180	25.8
0	KF0182	7.8
	MEAN	13.1
	SE	2.2

Table 4 continued on following page

TABLE 4

Individual Data Depicting the Effect of YRC 2894
 on Cervical Prostaglandin E₂ (PG E₂) Content in Female Rats on Lactation Day 2^a

Dose (ppm)	Animal Number	PG E ₂ (ng/gm cervix)
800	KF1105	19.0
800	KF1133	--- ^b
800	KF1143	---
800	KF1149	---
800	KF1150	23.5
800	KF1155	8.0
800	KF1169	6.5
800	KF1171	20.5
800	KF1173	8.0
800	KF1174	20.4
800	KF1183	13.0
800	KF1184	16.8
	MEAN	11.6
	SE	2.3

^a Cycling female rats were dosed with YRC 2894 for 8 ± 1 weeks; the animals were mated and exposure to the chemical continued through pregnancy and delivery, concluding at Day 2 of lactation. The YRC 2894 was administered to the animals as an admix to the diet, which was available for *ad libitum* consumption, at a constant concentration of either 0 or 800 ppm.

^b "---" indicates insufficient sample for analysis

TABLE 5

**Individual Data Depicting the Effect of YRC 2894
 on Cervical Prostaglandin F_{2α}(PG F_{2α}) Content in Cycling Rats^a**

Dose (ppm)	Animal Number	PG F _{2α} (ng/gm cervix)
0	KF0101	--- ^b
0	KF0107	87.0
0	KF0109	91.6
0	KF0113	72.6
0	KF0115	137.1
0	KF0118	---
0	KF0119	60.4
0	KF0120	98.6
0	KF0121	77.2
0	KF0122	---
0	KF0124	129.5
0	KF0126	117.5
0	KF0131	261.1
0	KF0133	206.7
0	KF0137	139.0
	MEAN	123.2
	SE	17.0

Table 5 continued on following page

TABLE 5

Individual Data Depicting the Effect of YRC 2894
on Cervical Prostaglandin F_{2α} (PG F_{2α}) Content in Cycling Rats^a

Dose (ppm)	Animal Number	PG F _{2α} (ng/gm cervix)
800	KF1101	54.8
800	KF1102	60.5
800	KF1103	138.4
800	KF1106	--- ^b
800	KF1107	71.9
800	KF1110	---
800	KF1113	---
800	KF1115	65.3
800	KF1116	307.5
800	KF1120	306.4
800	KF1123	110.7
800	KF1126	136.5
800	KF1132	114.2
800	KF1136	103.9
800	KF1138	59.4
	MEAN	127.5
	SE	25.7

^a Cycling female rats were dosed with YRC 2894 for 8 ± 1 consecutive weeks. The YRC 2894 was administered to the animals as an admix to the diet at a constant concentration of either 0 or 800 ppm. During the study, feed was available on a continuous basis for *ad libitum* consumption by the animals.

^b "---" indicates insufficient sample for analysis

TABLE 6

**Individual Data Depicting the Effect of YRC 2894
 on Cervical Prostaglandin F_{2α}(PG F_{2α}) Content in Pregnant Rats at Gestation Day 18^a**

Dose (ppm)	Animal Number	PG F _{2α} (ng/gm cervix)
0	KF0103	--- ^b
0	KF0104	---
0	KF0106	213.2
0	KF0108	281.9
0	KF0111	140.6
0	KF0116	---
0	KF0123	110.5
0	KF0132	76.9
0	KF0142	77.0
0	KF0147	71.2
0	KF0181	87.7
0	KF0183	84.7
0	KF0184	94.3
	MEAN	123.8
	SE	22.2

Table 6 continued on following page

TABLE 6

Individual Data Depicting the Effect of YRC 2894
on Cervical Prostaglandin F_{2α}(PG F_{2α}) Content in Pregnant Rats at Gestation Day 18^a

Dose (ppm)	Animal Number	PG F _{2α} (ng/gm cervix)
800	KF1108	--- ^b
800	KF1111	---
800	KF1114	114.5
800	KF1118	84.0
800	KF1127	---
800	KF1134	107.6
800	KF1135	85.5
800	KF1156	64.7
800	KF1159	102.4
800	KF1163	243.8
800	KF1165	246.1
	MEAN	131.1
	SE	25.5

^a Cycling female rats were dosed continuously with YRC 2894 for 8 ± 1 weeks; the animals were mated and exposure to the chemical continued up through Day 18 of gestation. The YRC 2894 was administered to the animals as an admix to the diet, which was available for *ad libitum* consumption, at a constant concentration of either 0 or 800 ppm.

^b "--" indicates insufficient sample for analysis

TABLE 7

Individual Data Depicting the Effect of YRC 2894
 on Cervical Prostaglandin F_{2α} (PG F_{2α}) Content in Pregnant Rats at Gestation Day 21^a

Dose (ppm)	Animal Number	PG F _{2α} (ng/gm cervix)
0	KF0110	--- ^b
0	KF0114	69.3
0	KF0134	33.7
0	KF0141	42.8
0	KF0143	69.5
0	KF0145	46.9
0	KF0146	58.1
0	KF0152	37.2
0	KF0153	54.4
0	KF0163	---
0	KF0165	---
0	KF0168	70.5
0	KF0169	69.2
0	KF0173	105.5
	MEAN	59.7
	SE	6.1

Table 7 continued on following page

TABLE 7

Individual Data Depicting the Effect of YRC 2894
on Cervical Prostaglandin F_{2α}(PG F_{2α}) Content in Pregnant Rats at Gestation Day 21^a

Dose (ppm)	Animal Number	PG F _{2α} (ng/gm cervix)
800	KF1112	70.6
800	KF1121	--- ^b
800	KF1122	---
800	KF1125	25.2
800	KF1128	---
800	KF1130	58.9
800	KF1137	32.3
800	KF1147	89.3
800	KF1162	47.9
800	KF1164	88.2
800	KF1167	58.0
800	KF1170	77.0
800	KF1175	51.6
800	KF1176	---
800	KF1179	---
800	KF1181	86.1
	MEAN	62.3
	SE	6.7

^a Cycling female rats were dosed continuously with YRC 2894 for 8 ± 1 weeks; the animals were mated and exposure to the chemical continued up through Day 21 of gestation. The YRC 2894 was administered to the animals as an admix to the diet, which was available *ad libitum* for consumption, at a constant concentration of either 0 or 800 ppm.

^b "---" indicates insufficient sample for analysis

TABLE 8

**Individual Data Depicting the Effect of YRC 2894
 on Cervical Prostaglandin F_{2α}(PG F_{2α}) Content in Female Rats on Lactation Day 2^a**

Dose (ppm)	Animal Number	PG F _{2α} (ng/gm cervix)
0	KF0105	64.9
0	KF0117	73.3
0	KF0136	27.7
0	KF0140	--- ^b
0	KF0148	42.1
0	KF0151	---
0	KF0156	---
0	KF0157	50.1
0	KF0160	55.5
0	KF0171	49.2
0	KF0174	49.3
0	KF0178	61.3
0	KF0180	78.4
0	KF0182	53.5
	MEAN	55.0
	SE	4.3

Table 8 continued on following page

TABLE 8

**Individual Data Depicting the Effect of YRC 2894
 on Cervical Prostaglandin F_{2α}(PG F_{2α}) Content in Female Rats on Lactation Day 2^a**

Dose (ppm)	Animal Number	PG F _{2α} (ng/gm cervix)
800	KF1105	53.9
800	KF1133	--- ^b
800	KF1143	---
800	KF1149	---
800	KF1150	64.8
800	KF1155	44.3
800	KF1169	22.5
800	KF1171	72.7
800	KF1173	54.5
800	KF1174	47.1
800	KF1183	35.7
800	KF1184	62.7
	MEAN	50.9
	SE	3.9

^a Cycling female rats were dosed with YRC 2894 for 8 ± 1 consecutive weeks; the animals were mated and exposure to the chemical continued through pregnancy and delivery, concluding at Day 2 of lactation. The YRC 2894 was administered to the animals as an admix to the diet, which was available *ad libitum* consumption, at a constant concentration of either 0 or 800 ppm.

^b "---" indicates insufficient sample for analysis

TABLE 9

**Individual Data Depicting the Effect of YRC 2894
 on Uterine Prostaglandin E₂ (PG E₂) Content in Cycling Rats^a**

Dose (ppm)	Animal Number	PG E ₂ (ng/gm uterus)
0	KF0101	--- ^b
0	KF0107	918.9
0	KF0109	708.5
0	KF0113	290.8
0	KF0115	520.8
0	KF0118	---
0	KF0119	438.9
0	KF0120	639.4
0	KF0121	87.8
0	KF0122	---
0	KF0124	329.9
0	KF0126	182.4
0	KF0131	2881.0
0	KF0133	1164.1
0	KF0137	118.6
	MEAN	690.1
	SE	220.3

Table 9 continued on following page

TABLE 9

Individual Data Depicting the Effect of YRC 2894
on Uterine Prostaglandin E₂ (PG E₂) Content in Cycling Rats^a

Dose (ppm)	Animal Number	PG E ₂ (ng/gm uterus)
800	KF1101	322.6
800	KF1102	136.4
800	KF1103	447.2
800	KF1106	--- ^b
800	KF1107	271.9
800	KF1110	---
800	KF1113	---
800	KF1115	112.6
800	KF1116	69.7
800	KF1120	53.9
800	KF1123	419.1
800	KF1126	237.6
800	KF1132	187.9
800	KF1136	1096.8
800	KF1138	1194.3
	MEAN	379.2
	SE	109.7

^a Cycling female rats were dosed with YRC 2894 for 8 ± 1 consecutive weeks. The YRC 2894 was administered to the animals as an admix to the diet at a constant concentration of either 0 or 800 ppm. During the study, feed was available on a continuous basis for *ad libitum* consumption by the animals.

^b "--" indicates insufficient sample for analysis

TABLE 10

Individual Data Depicting the Effect of YRC 2894
on Uterine Prostaglandin E₂ (PG E₂) Content in Pregnant Rats at Gestation Day 18^a

Dose (ppm)	Animal Number	PG E ₂ (ng/gm uterus)
0	KF0103	--- ^b
0	KF0104	---
0	KF0106	74.6
0	KF0108	102.7
0	KF0111	74.5
0	KF0116	---
0	KF0123	43.7
0	KF0132	66.6
0	KF0142	98.6
0	KF0147	53.0
0	KF0181	101.6
0	KF0183	99.8
0	KF0184	62.9
	MEAN	77.8
	SE	6.9

Table 10 continued on following page

TABLE 10

Individual Data Depicting the Effect of YRC 2894
on Uterine Prostaglandin E₂ (PG E₂) Content in Pregnant Rats at Gestation Day 18^a

Dose (ppm)	Animal Number	PG E ₂ (ng/gm uterus)
800	KF1108	--- ^b
800	KF1111	---
800	KF1114	113.4
800	KF1118	93.6
800	KF1127	---
800	KF1134	72.2
800	KF1135	74.3
800	KF1156	62.6
800	KF1159	65.2
800	KF1163	121.7
800	KF1165	101.1
	MEAN	88.0
	SE	8.0

^a Cycling female rats were dosed continuously with YRC 2894 for 8 ± 1 weeks; the animals were mated and exposure to the chemical continued up through Day 18 of gestation. The YRC 2894 was administered to the animals as an admix to the diet, which was available for *ad libitum* consumption, at a constant concentration of either 0 or 800 ppm.

^b "---" indicates insufficient sample for analysis

TABLE 11

Individual Data Depicting the Effect of YRC 2894
 on Uterine Prostaglandin E₂ (PG E₂) Content in Pregnant Rats at Gestation Day 21^a

Dose (ppm)	Animal Number	PG E ₂ (ng/gm uterus)
0	KF0110	---
0	KF0114	<i>b</i>
0	KF0134	8.7
0	KF0141	3.2
0	KF0143	3.4
0	KF0143	8.0
0	KF0145	2.0
0	KF0146	9.4
0	KF0152	10.8
0	KF0153	2.6
0	KF0163	---
0	KF0165	---
0	KF0168	8.2
0	KF0169	17.0
0	KF0173	13.3
	MEAN	7.9
	SE	1.4

Table 11 continued on following page

TABLE 11

Individual Data Depicting the Effect of YRC 2894
on Uterine Prostaglandin E₂ (PG E₂) Content in Pregnant Rats at Gestation Day 21^a

Dose (ppm)	Animal Number	PG E ₂ (ng/gm uterus)
800	KF1112	8.5
800	KF1121	--- ^b
800	KF1122	---
800	KF1125	10.0
800	KF1128	---
800	KF1130	19.0
800	KF1137	7.2
800	KF1147	9.9
800	KF1162	10.7
800	KF1164	12.1
800	KF1167	8.2
800	KF1170	7.9
800	KF1175	7.0
800	KF1176	---
800	KF1179	---
800	KF1181	6.7
	MEAN	9.7
	SE	1.1

^a Cycling female rats were dosed continuously with YRC 2894 for 8 ± 1 weeks; the animals were mated and exposure to the chemical continued up through Day 21 of gestation. The YRC 2894 was administered to the animals as an admix to the diet, which was available *ad libitum* consumption, at a constant concentration of either 0 or 800 ppm.

^b "---" indicates insufficient sample for analysis

TABLE 12

Individual Data Depicting the Effect of YRC 2894
on Uterine Prostaglandin E₂ (PG E₂) Content in Female Rats on Lactation Day 2^a

Dose (ppm)	Animal Number	PG E ₂ (ng/gm uterus)
0	KF0105	20.3
0	KF0117	23.4
0	KF0136	12.4
0	KF0140	--- ^b
0	KF0148	23.2
0	KF0151	---
0	KF0156	---
0	KF0157	10.6
0	KF0160	11.8
0	KF0171	9.1
0	KF0174	2.8
0	KF0178	5.1
0	KF0180	1.7
0	KF0182	8.6
	MEAN	11.7
	SE	2.3

Table 12 continued on following page

TABLE 12

Individual Data Depicting the Effect of YRC 2894
on Uterine Prostaglandin E₂ (PG E₂) Content in Female Rats on Lactation Day 2^a

Dose (ppm)	Animal Number	PG E ₂ (ng/gm uterus)
800	KF1105	20.0
800	KF1133	--- ^b
800	KF1143	---
800	KF1149	---
800	KF1150	12.2
800	KF1155	12.8
800	KF1169	17.7
800	KF1171	16.2
800	KF1173	10.1
800	KF1174	16.3
800	KF1183	7.5
800	KF1184	10.1
	MEAN	13.7
	SE	1.4

^a Cycling female rats were dosed continuously with YRC 2894 for 8 ± 1 weeks; the animals were mated and exposure to the chemical continued through pregnancy and delivery, concluding at Day 2 of lactation. The YRC 2894 was administered to the animals as an admix to the diet, which was available for *ad libitum* consumption, at a constant concentration of either 0 or 800 ppm.

^b "---" indicates insufficient sample for analysis

TABLE 13

**Individual Data Depicting the Effect of YRC 2894
 on Uterine Prostaglandin F_{2α}(PG F_{2α}) Content in Cycling Rats^a**

Dose (ppm)	Animal Number	PG F _{2α} (ng/gm uterus)
0	KF0101	--- ^b
0	KF0107	63.2
0	KF0109	118.9
0	KF0113	115.3
0	KF0115	72.7
0	KF0118	---
0	KF0119	111.5
0	KF0120	135.8
0	KF0121	73.1
0	KF0122	---
0	KF0124	98.3
0	KF0126	127.9
0	KF0131	192.8
0	KF0133	88.3
0	KF0137	98.8
	MEAN	108.1
	SE	10.1

Table 13 continued on following page

TABLE 13

Individual Data Depicting the Effect of YRC 2894
on Uterine Prostaglandin F_{2α}(PG F_{2α}) Content in Cycling Rats^a

Dose (ppm)	Animal Number	PG F _{2α} (ng/gm uterus)
800	KF1101	110.7
800	KF1102	100.0
800	KF1103	80.9
800	KF1106	97.9
800	KF1107	--- ^b
800	KF1110	---
800	KF1113	---
800	KF1115	155.1
800	KF1116	135.8
800	KF1120	162.7
800	KF1123	139.9
800	KF1126	107.8
800	KF1132	142.1
800	KF1136	80.4
800	KF1138	87.7
	MEAN	116.8
	SE	8.4

^a Cycling female rats were dosed with YRC 2894 for 8 ± 1 consecutive weeks. The YRC 2894 was administered to the animals as an admix to the diet at a constant concentration of either 0 or 800 ppm. During the study, feed was available on a continuous basis for *ad libitum* consumption by the animals.

^b "---" indicates insufficient sample for analysis

TABLE 14

Individual Data Depicting the Effect of YRC 2894
 on Uterine Prostaglandin F_{2α}(PG F_{2α}) Content in Pregnant Rats at Gestation Day 18^a

Dose (ppm)	Animal Number	PG F _{2α} (ng/gm uterus)
0	KF0103	--- ^b
0	KF0104	---
0	KF0106	141.5
0	KF0108	303.4
0	KF0111	153.2
0	KF0116	---
0	KF0123	98.1
0	KF0132	198.6
0	KF0142	241.9
0	KF0147	127.7
0	KF0181	191.0
0	KF0183	432.6
0	KF0184	250.6
	MEAN	213.9
	SE	31.4

Table 14 continued on following page

TABLE 14

Individual Data Depicting the Effect of YRC 2894
on Uterine Prostaglandin F_{2α}(PG F_{2α}) Content in Pregnant Rats at Gestation Day 18^a

Dose (ppm)	Animal Number	PG F _{2α} (ng/gm uterus)
800	KF1108	--- ^b
800	KF1111	---
800	KF1114	235.5
800	KF1118	469.9
800	KF1127	---
800	KF1134	283.5
800	KF1135	458.1
800	KF1156	205.1
800	KF1159	292.9
800	KF1163	962.8
800	KF1165	709.3
	MEAN	452.1 ^c
	SE	93.4

^a Cycling female rats were dosed continuously with YRC 2894 for 8 ± 1 weeks; the animals were mated and exposure to the chemical continued up through Day 18 of gestation. The YRC 2894 was administered to the animals as an admix to the diet, which was available for *ad libitum* consumption, at a constant concentration of either 0 or 800 ppm.

^b "---" indicates insufficient sample for analysis

^c Indicates statistically significant difference from control by Student's t-test (unpaired); p ≤ 0.05.

TABLE 15

Individual Data Depicting the Effect of YRC 2894
on Uterine Prostaglandin F_{2α}(PG F_{2α}) Content in Pregnant Rats at Gestation Day 21^a

Dose (ppm)	Animal Number	PG F _{2α} (ng/gm uterus)
0	KF0110	--- ^b
0	KF0114	279.2
0	KF0134	137.3
0	KF0141	183.6
0	KF0143	191.0
0	KF0145	85.0
0	KF0146	313.0
0	KF0152	152.7
0	KF0153	106.1
0	KF0163	---
0	KF0165	---
0	KF0168	223.6
0	KF0169	521.2
0	KF0173	324.5
	MEAN	228.8
	SE	37.9

Table 15 continued on following page

TABLE 15

Individual Data Depicting the Effect of YRC 2894
on Uterine Prostaglandin F_{2α}(PG F_{2α}) Content in Pregnant Rats at Gestation Day 21^a

Dose (ppm)	Animal Number	PG F _{2α} (ng/gm uterus)
800	KF1112	254.7
800	KF1121	--- ^b
800	KF1122	---
800	KF1125	277.4
800	KF1128	---
800	KF1130	498.7
800	KF1137	161.5
800	KF1147	101.5
800	KF1162	165.4
800	KF1164	275.6
800	KF1167	159.4
800	KF1170	231.8
800	KF1175	---
800	KF1176	---
800	KF1179	---
800	KF1181	243.2
	MEAN	236.9
	SE	34.5

^a Cycling female rats were dosed continuously with YRC 2894 for 8 ± 1 weeks; the animals were mated and exposure to the chemical continued up through Day 21 of gestation. The YRC 2894 was administered to the animals as an admix to the diet, which was available for *ad libitum* consumption, at a constant concentration of either 0 or 800 ppm.

^b "--" indicates insufficient sample for analysis

TABLE 16

**Individual Data Depicting the Effect of YRC 2894
 on Uterine Prostaglandin F_{2α}(PG F_{2α}) Content in Female Rats on Lactation Day 2^a**

Dose (ppm)	Animal Number	PG F _{2α} (ng/gm uterus)
0	KF0105	158.5
0	KF0117	147.6
0	KF0136	130.4
0	KF0140	--- ^b
0	KF0148	122.3
0	KF0151	---
0	KF0156	---
0	KF0157	113.7
0	KF0160	108.0
0	KF0171	124.9
0	KF0174	91.9
0	KF0178	94.0
0	KF0180	98.9
0	KF0182	136.6
	MEAN	120.6
	SE	6.6

Table 16 continued on following page

TABLE 16

Individual Data Depicting the Effect of YRC 2894
on Uterine Prostaglandin F_{2α}(PG F_{2α}) Content in Female Rats on Lactation Day 2^a

Dose (ppm)	Animal Number	PG F _{2α} (ng/gm uterus)
800	KF1105	94.1
800	KF1133	--- ^b
800	KF1143	---
800	KF1149	---
800	KF1150	94.7
800	KF1155	86.1
800	KF1169	194.1
800	KF1171	177.0
800	KF1173	210.1
800	KF1174	211.5
800	KF1183	67.6
800	KF1184	102.0
	MEAN	137.5
	SE	19.7

^a Cycling female rats were dosed continuously with YRC 2894 for 8 ± 1 weeks; the animals were mated and exposure to the chemical continued through pregnancy and delivery, concluding at Day 2 of lactation. The YRC 2894 was administered to the animals as an admix to the diet, which was available for *ad libitum* consumption, at a constant concentration of either 0 or 800 ppm.

^b "---" indicates insufficient sample for analysis

TABLE 17

Individual Data Depicting the Effect of YRC 2894
on Circulating Follicle Stimulating Hormone (FSH) Content in Cycling Rats^a

Dose (ppm)	Animal Number	FSH (ng/mL serum)
0	KF0101	2.40
0	KF0107	2.85
0	KF0109	2.50
0	KF0113	2.45
0	KF0115	3.45
0	KF0118	3.25
0	KF0119	2.90
0	KF0120	2.15
0	KF0121	2.80
0	KF0122	3.25
0	KF0124	1.35
0	KF0126	2.30
0	KF0131	2.70
0	KF0133	2.75
0	KF0137	2.00
	MEAN	2.60
	SE	0.14

Table 17 continued on following page

TABLE 17

Individual Data Depicting the Effect of YRC 2894
on Circulating Follicle Stimulating Hormone (FSH) Content in Cycling Rats^a

Dose (ppm)	Animal Number	FSH (ng/mL serum)
800	KF1101	2.65
800	KF1102	2.90
800	KF1103	3.40
800	KF1106	2.90
800	KF1107	2.75
800	KF1110	2.40
800	KF1113	2.35
800	KF1115	3.30
800	KF1116	2.45
800	KF1120	2.65
800	KF1123	2.65
800	KF1126	--- ^b
800	KF1132	2.80
800	KF1136	2.65
800	KF1138	3.20
	MEAN	2.79
	SE	0.09

^a Cycling female rats were dosed with YRC 2894 for 8 ± 1 consecutive weeks. The YRC 2894 was administered to the animals as an admix to the diet at a constant concentration of either 0 or 800 ppm. During the study, feed was available on a continuous basis for *ad libitum* consumption by the animals.

^b "--" indicates insufficient sample for analysis

TABLE 18

Individual Data Depicting the Effect of YRC 2894
on Circulating Follicle Stimulating Hormone (FSH) Content
in Pregnant Rats at Gestation Day 18^a

Dose (ppm)	Animal Number	FSH (ng/mL serum)
0	KF0103	3.80
0	KF0104	4.25
0	KF0106	2.35
0	KF0108	3.40
0	KF0111	2.75
0	KF0116	2.80
0	KF0123	4.40
0	KF0132	3.15
0	KF0142	3.25
0	KF0147	2.65
0	KF0181	1.90
0	KF0183	3.75
0	KF0184	1.75
	MEAN	3.09
	SE	0.23

Table 18 continued on following page

TABLE 18

Individual Data Depicting the Effect of YRC 2894
 on Circulating Follicle Stimulating Hormone (FSH) Content
 in Pregnant Rats at Gestation Day 18^a

Dose (ppm)	Animal Number	FSH (ng/mL serum)
800	KF1108	3.10
800	KF1111	3.90
800	KF1114	3.55
800	KF1118	3.15
800	KF1127	3.10
800	KF1134	4.35
800	KF1135	3.05
800	KF1156	3.35
800	KF1159	3.30
800	KF1163	4.20
800	KF1165	3.95
	MEAN	3.55
	SE	0.14

^a Cycling female rats were dosed continuously with YRC 2894 for 8 ± 1 weeks; the animals were mated and exposure to the chemical continued up through Day 18 of gestation. The YRC 2894 was administered to the animals as an admix to the diet, which was available for *ad libitum* consumption, at a constant concentration of either 0 or 800 ppm.

^b "--" indicates insufficient sample for analysis

TABLE 19

**Individual Data Depicting the Effect of YRC 2894
on Circulating Follicle Stimulating Hormone (FSH) Content
in Female Rats on Lactation Day 2^a**

Dose (ppm)	Animal Number	FSH (ng/mL serum)
0	KF0105	2.35
0	KF0117	3.15
0	KF0136	2.60
0	KF0140	2.30
0	KF0148	3.35
0	KF0151	2.30
0	KF0156	--- ^b
0	KF0157	3.30
0	KF0160	2.25
0	KF0171	3.65
0	KF0174	2.70
0	KF0178	2.35
0	KF0180	2.30
0	KF0182	2.10
	MEAN	2.67
	SE	0.14

Table 19 continued on following page

TABLE 19

Individual Data Depicting the Effect of YRC 2894
on Circulating Follicle Stimulating Hormone (FSH) Content
in Female Rats on Lactation Day 2^a

Dose (ppm)	Animal Number	FSH (ng/mL serum)
800	KF1105	2.15
800	KF1133	2.15
800	KF1143	3.10
800	KF1149	3.80
800	KF1150	2.80
800	KF1155	2.00
800	KF1169	3.30
800	KF1171	4.25
800	KF1173	1.55
800	KF1174	2.50
800	KF1183	3.80
800	KF1184	2.50
	MEAN	2.83
	SE	0.24

^a Cycling female rats were dosed continuously with YRC 2894 for 8 ± 1 weeks; the animals were mated and exposure to the chemical continued through pregnancy and delivery, concluding at Day 2 of lactation. The YRC 2894 was administered to the animals as an admix to the diet, which was available for *ad libitum* consumption, at a constant concentration of either 0 or 800 ppm.

^b "--" indicates insufficient sample for analysis

TABLE 20

Individual Data Depicting the Effect of YRC 2894
 on Circulating Lutenizing Hormone (LH) in Cycling Rats^a

Dose (ppm)	Animal Number	LH (ng/mL serum)
0	KF0101	0.55
0	KF0107	0.85
0	KF0109	0.55
0	KF0113	0.50
0	KF0115	0.45
0	KF0118	0.95
0	KF0119	0.45
0	KF0120	0.10
0	KF0121	0.25
0	KF0122	0.55
0	KF0124	1.75
0	KF0126	0.65
0	KF0131	0.80
0	KF0133	0.50
0	KF0137	1.30
	MEAN	0.68
	SE	0.11

Table 20 continued on following page

TABLE 20

Individual Data Depicting the Effect of YRC 2894
on Circulating Lutenizing Hormone (LH) in Cycling Rats^a

Dose (ppm)	Animal Number	LH (ng/mL serum)
800	KF1101	0.80
800	KF1102	1.20
800	KF1103	1.10
800	KF1106	1.70
800	KF1107	1.35
800	KF1110	1.30
800	KF1113	0.85
800	KF1115	1.50
800	KF1116	1.30
800	KF1120	0.30
800	KF1123	0.75
800	KF1126	--- ^b
800	KF1132	0.85
800	KF1136	0.75
800	KF1138	0.90
	MEAN	1.05 ^c
	SE	0.10

^a Cycling female rats were dosed with YRC 2894 for 8 ± 1 consecutive weeks. The YRC 2894 was administered to the animals as an admix to the diet at a constant concentration of either 0 or 800 ppm. During the study, feed was available on a continuous basis for *ad libitum* consumption by the animals.

^b "---" indicates insufficient sample for analysis

^c Indicates statistically significant difference from control by Student's t-test (unpaired); $p \leq 0.05$.

TABLE 21

Individual Data Depicting the Effect of YRC 2894
on Circulating Lutenizing Hormone (LH) in Pregnant Rats at Gestation Day 18^a

Dose (ppm)	Animal Number	LH (ng/mL serum)
0	KF0103	1.10
0	KF0104	1.40
0	KF0106	0.15
0	KF0108	0.15
0	KF0111	0.30
0	KF0116	0.20
0	KF0123	0.30
0	KF0132	0.15
0	KF0142	0.50
0	KF0147	1.05
0	KF0181	0.20
0	KF0183	0.25
0	KF0184	0.25
	MEAN	0.46
	SE	0.12

Table 21 continued on following page

TABLE 21

Individual Data Depicting the Effect of YRC 2894
 on Circulating Lutenizing Hormone (LH) in Pregnant Rats at Gestation Day 18^a

Dose (ppm)	Animal Number	LH (ng/mL serum)
800	KF1108	0.20
800	KF1111	2.15
800	KF1114	0.20
800	KF1118	0.75
800	KF1127	1.00
800	KF1134	1.70
800	KF1135	0.40
800	KF1156	0.95
800	KF1159	0.80
800	KF1163	0.25
800	KF1165	1.15
	MEAN	0.87
	SE	0.19

^a Cycling female rats were dosed continuously with YRC 2894 for 8 ± 1 weeks; the animals were mated and exposure to the chemical continued up through Day 18 of gestation. The YRC 2894 was administered to the animals as an admix to the diet, which was available for *ad libitum* consumption, at a constant concentration of either 0 or 800 ppm.

TABLE 22

Individual Data Depicting the Effect of YRC 2894
 on Circulating Lutenizing Hormone (LH) in Female Rats on Lactation Day 2^a

Dose (ppm)	Animal Number	LH (ng/mL serum)
0	KF0105	--- ^b
0	KF0117	0.40
0	KF0136	0.40
0	KF0140	0.25
0	KF0148	0.50
0	KF0151	0.00
0	KF0156	0.15
0	KF0157	0.30
0	KF0160	0.30
0	KF0171	0.20
0	KF0174	0.15
0	KF0178	0.35
0	KF0180	0.15
0	KF0182	0.30
	MEAN	0.27
	SE	0.04

Table 22 continued on following page

TABLE 22

Individual Data Depicting the Effect of YRC 2894
on Circulating Lutenizing Hormone (LH) in Female Rats on Lactation Day 2^a

Dose (ppm)	Animal Number	LH (ng/mL serum)
800	KF1105	0.40
800	KF1133	0.30
800	KF1143	0.40
800	KF1149	0.60
800	KF1150	0.35
800	KF1155	0.25
800	KF1169	0.80
800	KF1171	0.20
800	KF1173	0.85
800	KF1174	0.45
800	KF1183	0.25
800	KF1184	1.35
	MEAN	0.52 ^c
	SE	0.10

^a Cycling female rats were dosed continuously with YRC 2894 for 8 ± 1 weeks; the animals were mated and exposure to the chemical continued through pregnancy and delivery, concluding at Day 2 of lactation. The YRC 2894 was administered to the animals as an admix to the diet, which was available for *ad libitum* consumption, at a constant concentration of either 0 or 800 ppm.

^b "--" indicates insufficient sample for analysis

^c Indicates statistically significant difference from control by Student's t-test (unpaired); $p \leq 0.05$.

TABLE 23

Individual Data Depicting the Effect of YRC 2894
on Circulating 17 β -Estradiol (E₂) in Cycling Rats^a

Dose (ppm)	Animal Number	E ₂ (pg/mL serum)
0	KF0101	59.24
0	KF0107	43.20
0	KF0109	23.76
0	KF0113	35.04
0	KF0115	33.76
0	KF0118	16.92
0	KF0119	13.64
0	KF0120	16.88
0	KF0121	47.64
0	KF0122	35.32
0	KF0124	35.92
0	KF0126	31.20
0	KF0131	39.52
0	KF0133	16.52
0	KF0137	67.04
	MEAN	34.37
	SE	4.05

Table 23 continued on following page

TABLE 23

Individual Data Depicting the Effect of YRC 2894
on Circulating 17 β -Estradiol (E₂) in Cycling Rats^a

Dose (ppm)	Animal Number	E ₂ (pg/mL serum)
800	KF1101	52.24
800	KF1102	72.92
800	KF1103	32.76
800	KF1106	57.96
800	KF1107	57.04
800	KF1110	38.04
800	KF1113	34.24
800	KF1115	67.84
800	KF1116	41.80
800	KF1120	31.88
800	KF1123	35.24
800	KF1126	61.32
800	KF1132	57.76
800	KF1136	37.48
800	KF1138	43.32
	MEAN	48.12 ^b
	SE	3.52

^a Cycling female rats were dosed with YRC 2894 for 8 \pm 1 consecutive weeks. The YRC 2894 was administered to the animals as an admix to the diet at a constant concentration of either 0 or 800 ppm. During the study, feed was available on a continuous basis for *ad libitum* consumption by the animals.

^b Indicates statistically significant difference from control by Student's t-test (unpaired); $p \leq 0.05$.

TABLE 24

Individual Data Depicting the Effect of YRC 2894
on Circulating 17 β -Estradiol (E₂) in Pregnant Rats at Gestation Day 18^a

Dose (ppm)	Animal Number	E ₂ (pg/mL serum)
0	KF0103	28.68
0	KF0104	21.84
0	KF0106	86.08
0	KF0108	43.44
0	KF0111	36.04
0	KF0116	25.68
0	KF0123	4.12
0	KF0132	29.08
0	KF0142	22.80
0	KF0147	63.12
0	KF0181	28.88
0	KF0183	8.80
0	KF0184	8.56
	MEAN	31.32
	SE	6.28

Table 24 continued on following page

TABLE 24

Individual Data Depicting the Effect of YRC 2894
 on Circulating 17 β -Estradiol (E₂) in Pregnant Rats at Gestation Day 18^a

Dose (ppm)	Animal Number	E ₂ (pg/mL serum)
800	KF1108	44.04
800	KF1111	35.68
800	KF1114	74.04
800	KF1118	21.92
800	KF1127	40.16
800	KF1134	22.92
800	KF1135	53.60
800	KF1156	31.72
800	KF1159	16.24
800	KF1163	50.56
800	KF1165	44.72
	MEAN	39.60
	SE	5.01

^a Cycling female rats were dosed continuously with YRC 2894 for 8 \pm 1 weeks; the animals were mated and exposure to the chemical continued up through Day 18 of gestation. The YRC 2894 was administered to the animals as an admix to the diet, which was available for *ad libitum* consumption, at a constant concentration of either 0 or 800 ppm.

TABLE 25

Individual Data Depicting the Effect of YRC 2894
 on Circulating 17 β -Estradiol (E₂) in Female Rats on Lactation Day 2^a

Dose (ppm)	Animal Number	E ₂ (pg/mL serum)
0	KF0105	16.16
0	KF0117	12.00
0	KF0136	13.88
0	KF0140	22.44
0	KF0148	21.48
0	KF0151	8.56
0	KF0156	12.88
0	KF0157	20.48
0	KF0160	12.08
0	KF0171	23.40
0	KF0174	28.20
0	KF0178	24.48
0	KF0180	35.56
0	KF0182	19.32
	MEAN	19.35
	SE	1.97

Table 25 continued on following page

TABLE 25

Individual Data Depicting the Effect of YRC 2894
on Circulating 17 β -Estradiol (E₂) in Female Rats on Lactation Day 2^a

Dose (ppm)	Animal Number	E ₂ (pg/mL serum)
800	KF1105	62.44
800	KF1133	30.40
800	KF1143	29.92
800	KF1149	79.12
800	KF1150	23.12
800	KF1155	23.72
800	KF1169	37.52
800	KF1171	103.28
800	KF1173	59.36
800	KF1174	42.88
800	KF1183	68.88
800	KF1184	23.16
	MEAN	48.65 ^b
	SE	7.48

^a Cycling female rats were dosed continuously with YRC 2894 for 8 \pm 1 weeks; the animals were mated and exposure to the chemical continued through pregnancy and delivery, concluding at Day 2 of lactation. The YRC 2894 was administered to the animals as an admix to the diet, which was available for *ad libitum* consumption, at a constant concentration of either 0 or 800 ppm.

^b Indicates statistically significant difference from control by Student's t-test (unpaired); $p \leq 0.05$.

TABLE 26

Individual Data Depicting the Effect of YRC 2894
on Circulating Corticosterone (CORST) in Cycling Rats^a

Dose (ppm)	Animal Number	CORST (ng/mL serum)
0	KF0101	96.52
0	KF0107	286.52
0	KF0109	385.64
0	KF0113	150.78
0	KF0115	394.97
0	KF0118	434.52
0	KF0119	40.44
0	KF0120	337.45
0	KF0121	419.72
0	KF0122	314.19
0	KF0124	329.52
0	KF0126	447.61
0	KF0131	311.31
0	KF0133	205.61
0	KF0137	595.42
	MEAN	316.7
	SE	37.6

Table 26 continued on following page

TABLE 26

Individual Data Depicting the Effect of YRC 2894
on Circulating Corticosterone (CORST) in Cycling Rats^a

Dose (ppm)	Animal Number	CORST (ng/mL serum)
800	KF1101	463.16
800	KF1102	648.03
800	KF1103	513.40
800	KF1106	455.10
800	KF1107	373.45
800	KF1110	461.57
800	KF1113	364.84
800	KF1115	630.71
800	KF1116	464.01
800	KF1120	497.23
800	KF1123	414.02
800	KF1126	--- ^b
800	KF1132	493.08
800	KF1136	431.13
800	KF1138	488.77
	MEAN	478.46 ^c
	SE	21.67

^a Cycling female rats were dosed with YRC 2894 for 8 ± 1 consecutive weeks. The YRC 2894 was administered to the animals as an admix to the diet at a constant concentration of either 0 or 800 ppm. During the study, feed was available on a continuous basis for *ad libitum* consumption by the animals.

^b "---" indicates insufficient sample for analysis

^c Indicates statistically significant difference from control by Student's t-test (unpaired); $p \leq 0.05$.

TABLE 27

Individual Data Depicting the Effect of YRC 2894
on Circulating Corticosterone (CORST) in Pregnant Rats at Gestation Day 18^a

Dose (ppm)	Animal Number	CORST (ng/mL serum)
0	KF0103	92.49
0	KF0104	113.71
0	KF0106	402.45
0	KF0108	366.17
0	KF0111	264.29
0	KF0116	249.94
0	KF0123	177.70
0	KF0132	198.24
0	KF0142	118.08
0	KF0147	256.16
0	KF0181	326.77
0	KF0183	274.98
0	KF0184	85.94
	MEAN	225.15
	SE	28.99

Table 27 continued on following page

TABLE 27

Individual Data Depicting the Effect of YRC 2894
on Circulating Corticosterone (CORST) in Pregnant Rats at Gestation Day 18^a

Dose (ppm)	Animal Number	CORST (ng/mL serum)
800	KF1108	229.24
800	KF1111	361.74
800	KF1114	357.45
800	KF1118	494.47
800	KF1127	451.87
800	KF1134	600.17
800	KF1135	92.35
800	KF1156	417.29
800	KF1159	235.14
800	KF1163	380.22
800	KF1165	742.48
	MEAN	396.58 ^b
	SE	54.26

^a Cycling female rats were dosed continuously with YRC 2894 for 8 ± 1 weeks; the animals were mated and exposure to the chemical continued up through Day 18 of gestation. The YRC 2894 was administered to the animals as an admix to the diet, which was available for *ad libitum* consumption, at a constant concentration of either 0 or 800 ppm.

^b Indicates statistically significant difference from control by Student's t-test (unpaired); $p \leq 0.05$.

TABLE 28

**Individual Data Depicting the Effect of YRC 2894
 on Circulating Cortiosterone (CORST) in Female Rats on Lactation Day 2^a**

Dose (ppm)	Animal Number	CORST (ng/mL serum)
0	KF0105	79.42
0	KF0117	235.80
0	KF0136	329.62
0	KF0140	330.49
0	KF0148	324.11
0	KF0151	316.38
0	KF0156	--- ^b
0	KF0157	288.60
0	KF0160	247.69
0	KF0171	133.94
0	KF0174	240.44
0	KF0178	321.21
0	KF0180	235.14
0	KF0182	360.04
	MEAN	264.84
	SE	22.87

Table 28 continued on following page

TABLE 28

Individual Data Depicting the Effect of YRC 2894
on Circulating Corticosterone (CORST) in Female Rats on Lactation Day 2^a

Dose (ppm)	Animal Number	CORST (ng/mL serum)
800	KF1105	335.27
800	KF1133	398.13
800	KF1143	467.91
800	KF1149	380.43
800	KF1150	369.25
800	KF1155	310.79
800	KF1169	335.62
800	KF1171	433.99
800	KF1173	539.61
800	KF1174	511.14
800	KF1183	344.51
800	KF1184	271.64
	MEAN	391.52 ^c
	SE	23.67

^a Cycling female rats were dosed continuously with YRC 2894 for 8 ± 1 weeks; the animals were mated and exposure to the chemical continued through pregnancy and delivery, concluding at Day 2 of lactation. The YRC 2894 was administered to the animals as an admix to the diet, which was available for *ad libitum* consumption, at a constant concentration of either 0 or 800 ppm.

^b "--" indicates insufficient sample for analysis

^c Indicates statistically significant difference from control by Student's t-test (unpaired); $p \leq 0.05$.

TABLE 29

**Individual Data Depicting the Effect of YRC 2894
 on Circulating Oxytocin in Pregnant Rats at Gestation Day 21^a**

Dose (ppm)	Animal Number	Oxytocin (ng/mL plasma)
0	KF0110	2.05
0	KF0114	1.24
0	KF0134	0.79
0	KF0141	3.15
0	KF0143	1.95
0	KF0145	1.52
0	KF0146	1.81
0	KF0152	1.12
0	KF0153	1.07
0	KF0163	0.12
0	KF0165	1.57
0	KF0168	0.50
0	KF0169	0.88
0	KF0173	0.07
	MEAN	1.27
	SE	0.22

Table 29 continued on following page

TABLE 29

Individual Data Depicting the Effect of YRC 2894
on Circulating Oxytocin in Pregnant Rats at Gestation Day 21^a

Dose (ppm)	Animal Number	Oxytocin (ng/mL plasma)
800	KF1112	6.48
800	KF1121	0.89
800	KF1122	1.70
800	KF1125	1.52
800	KF1128	0.92
800	KF1130	1.46
800	KF1137	1.14
800	KF1147	1.45
800	KF1162	0.84
800	KF1164	1.00
800	KF1167	0.27
800	KF1170	1.57
800	KF1175	1.15
800	KF1176	0.68
800	KF1179	1.21
800	KF1181	0.50
	MEAN	1.42
	SE	0.35

^a Cycling female rats were dosed continuously with YRC 2894 for 8 ± 1 weeks; the animals were mated and exposure to the chemical continued up through Day 21 of gestation. The YRC 2894 was administered to the animals as an admix to the diet, which was available for *ad libitum* consumption, at a constant concentration of either 0 or 800 ppm.

TABLE 30

Individual Data Depicting the Effect of YRC 2894
on Circulating Prolactin in Cycling Rats^a

Dose (ppm)	Animal Number	Prolactin (ng/mL serum)
0	KF0101	2.60
0	KF0107	3.00
0	KF0109	4.65
0	KF0113	1.35
0	KF0115	24.20
0	KF0118	12.60
0	KF0119	2.30
0	KF0120	46.80
0	KF0121	5.30
0	KF0122	3.35
0	KF0124	15.95
0	KF0126	10.30
0	KF0131	7.15
0	KF0133	1.75
0	KF0137	--- ^c
	MEAN	10.09
	SE	3.32

Table 30 continued on following page

TABLE 30

Individual Data Depicting the Effect of YRC 2894
on Circulating Prolactin in Cycling Rats^a

Dose (ppm)	Animal Number	Prolactin (ng/mL serum)
800	KF1101	3.90
800	KF1102	7.30
800	KF1103	--- ^b
800	KF1106	10.75
800	KF1107	2.85
800	KF1110	24.85
800	KF1113	--- ^b
800	KF1115	3.95
800	KF1116	--- ^b
800	KF1120	1.75
800	KF1123	--- ^b
800	KF1126	--- ^b
800	KF1132	7.30
800	KF1136	7.20
800	KF1138	2.10
	MEAN	7.20
	SE	2.16

^a Cycling female rats were dosed with YRC 2894 for 8 ± 1 weeks. The YRC 2894 was administered to the animals as an admix to the diet at a constant concentration of either 0 or 800 ppm. During the study, feed was available on a continuous basis for *ad libitum* consumption by the animals.

^b "---" indicates insufficient sample for analysis

^c "---" indicates sample result was outside of prolactin standard curve range

TABLE 31

Individual Data Depicting the Effect of YRC 2894
 on Circulating Prolactin in Pregnant Rats at Gestation Day 18^a

Dose (ppm)	Animal Number	Prolactin (ng/mL serum)
0	KF0103	47.90
0	KF0104	51.00
0	KF0106	5.10
0	KF0108	18.10
0	KF0111	15.20
0	KF0116	14.60
0	KF0123	25.20
0	KF0132	21.10
0	KF0142	--- ^b
0	KF0147	35.00
0	KF0181	29.40
0	KF0183	6.80
0	KF0184	45.00
	MEAN	26.20
	SE	4.52

Table 31 continued on following page

TABLE 31

Individual Data Depicting the Effect of YRC 2894
 on Circulating Prolactin in Pregnant Rats at Gestation Day 18^a

Dose (ppm)	Animal Number	Prolactin (ng/mL serum)
800	KF1108	12.30
800	KF1111	30.50
800	KF1114	2.90
800	KF1118	9.90
800	KF1127	29.20
800	KF1134	60.40
800	KF1135	9.00
800	KF1156	39.20
800	KF1159	--- ^b
800	KF1163	5.60
800	KF1165	---
	MEAN	22.11
	SE	6.39

^a Cycling female rats were dosed continuously with YRC 2894 for 8 ± 1 weeks; the animals were mated and exposure to the chemical continued up through Day 18 of gestation. The YRC 2894 was administered to the animals as an admix to the diet, which was available for *ad libitum* consumption, at a constant concentration of either 0 or 800 ppm.

^b "---" indicates sample result was outside of prolactin standard curve range

TABLE 32

Individual Data Depicting the Effect of YRC 2894
 on Circulating Prolactin in Female Rats on Lactation Day 2^a

Dose (ppm)	Animal Number	Prolactin (ng/mL serum)
0	KF0105	--- <i>b</i>
0	KF0117	--- <i>c</i>
0	KF0136	--- <i>c</i>
0	KF0140	36.40
0	KF0148	--- <i>c</i>
0	KF0151	22.90
0	KF0156	--- <i>b</i>
0	KF0157	--- <i>c</i>
0	KF0160	58.80
0	KF0171	39.70
0	KF0174	26.60
0	KF0178	--- <i>c</i>
0	KF0180	--- <i>b</i>
0	KF0182	--- <i>c</i>
	MEAN	36.88
	SE	6.28

Table 32 continued on following page

TABLE 32

Individual Data Depicting the Effect of YRC 2894
on Circulating Prolactin in Female Rats on Lactation Day 2^a

Dose (ppm)	Animal Number	Prolactin (ng/mL serum)
800	KF1105	30.30
800	KF1133	43.90
800	KF1143	24.70
800	KF1149	13.70
800	KF1150	27.80
800	KF1155	22.80
800	KF1169	--- ^c
800	KF1171	ND ^d
800	KF1173	--- ^c
800	KF1174	--- ^b
800	KF1183	--- ^c
800	KF1184	--- ^b
	MEAN	27.20
	SE	4.10

^a Cycling female rats were dosed continuously with YRC 2894 for 8 ± 1 weeks; the animals were mated and exposure to the chemical continued through pregnancy and delivery, concluding at Day 2 of lactation. The YRC 2894 was administered to the animals as an admix to the diet, which was available for *ad libitum* consumption, at a constant concentration of either 0 or 800 ppm.

^b "---" indicates insufficient sample for analysis

^c "---" indicates sample result was outside of prolactin standard curve range

^d ND = Not determined

TABLE 33

**Individual Data Depicting the Effect of YRC 2894
on Circulating Progesterone in Cycling Rats^a**

Dose (ppm)	Animal Number	Progesterone (ng/mL serum)
0	KF0101	18.23
0	KF0107	9.61
0	KF0109	21.02
0	KF0113	17.71
0	KF0115	36.56
0	KF0118	26.77
0	KF0119	9.22
0	KF0120	26.79
0	KF0121	29.39
0	KF0122	16.22
0	KF0124	23.13
0	KF0126	26.29
0	KF0131	23.99
0	KF0133	10.18
0	KF0137	12.35
	MEAN	20.50
	SE	2.09

Table 33 continued on following page

TABLE 33

Individual Data Depicting the Effect of YRC 2894
 on Circulating Progesterone in Cycling Rats^a

Dose (ppm)	Animal Number	Progesterone (ng/mL serum)
800	KF1101	21.83
800	KF1102	44.95
800	KF1103	22.29
800	KF1106	21.15
800	KF1107	13.42
800	KF1110	38.82
800	KF1113	8.30
800	KF1115	34.66
800	KF1116	32.25
800	KF1120	13.94
800	KF1123	21.55
800	KF1126	15.27
800	KF1132	30.72
800	KF1136	9.61
800	KF1138	26.33
	MEAN	23.67
	SE	2.81

^a Cycling female rats were dosed continuously with YRC 2894 for 8 ± 1 weeks. The YRC 2894 was administered to the animals as an admix to the diet at a constant concentration of either 0 or 800 ppm. During the study, feed was available on a continuous basis for *ad libitum* consumption by the animals.

TABLE 34

Individual Data Depicting the Effect of YRC 2894
on Circulating Progesterone in Pregnant Rats at Gestation Day 18^a

Dose (ppm)	Animal Number	Progesterone (ng/mL serum)
0	KF0103	61.32
0	KF0104	66.22
0	KF0106	85.44
0	KF0108	86.20
0	KF0111	62.02
0	KF0116	65.94
0	KF0123	43.63
0	KF0132	84.36
0	KF0142	84.80
0	KF0147	88.16
0	KF0181	91.40
0	KF0183	66.07
0	KF0184	59.90
	MEAN	72.73
	SE	4.08

Table 34 continued on following page