

## The effect of cyfluthrin, a commercially available synthetic pyrethroid, on bovine semen quality and pregnancy rates

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### Abstract

Reports of research in laboratory animals and clinical case studies in livestock suggest pyrethroids may reduce fertility. The objective of the experiments reported here was to assess the effects of cyfluthrin on cattle reproduction. In experiment 1 Angus x Simmental bulls were allocated to the following treatments: control with no pesticide applied (n=5), cyfluthrin pour-on (n=5), cyfluthrin fly tag (n=7), and cyfluthrin pour-on plus fly tag (n=7). Semen was collected weekly for nine weeks and analyzed for overall sperm motility, progressive sperm motility, and sperm morphology with the aid of computer-assisted semen analysis. Blood samples were taken weekly at the time of semen collection and properly stored until testosterone concentrations could be assayed. There were no differences in overall motility (p=0.41), progressive motility (p=0.60) or morphology (p=0.41) among treatments. Mean testosterone concentrations did not differ (p=0.16) between control and treated bulls. In experiment 2 Angus and crossbred cows were synchronized for an artificial insemination (AI) program and randomly assigned to a control (n=61) or treated group (n=62). The treated group received both pour-on and fly tags at label doses. Insecticide was applied to the treated group at the time of controlled internal drug release (CIDR) insertion. Blood samples for progesterone analysis were collected on days 10 and 17 following timed AI. Pregnancy status was assessed 35 days after AI. The treated group had lower (p=0.02) progesterone concentrations on day 10 but not on day 17 (p=0.57). No differences (p=0.65) were observed in pregnancy rates between treatments. Reproductive parameters measured in bulls were not affected by cyfluthrin pour-ons or fly tags, even when used in combination. Transient effects were observed in the concentration of progesterone in the plasma of cows, but did not result in differences in pregnancy rates observed at 35 days of gestation.

**Keywords:** Cyfluthrin, pyrethroid, insecticide, reproduction, cattle

### Introduction

Pyrethroids are included in over 3500 registered insecticide products,<sup>1</sup> many of which are commonly used on or around cattle. Products such as ear tags, pour-ons and dusts combat pests such as flies, lice and ticks. Pyrethroids prolong the opening of sodium channels when a nerve is excited, thereby paralyzing the insect. The use of pyrethroids has increased during the past decade as the more toxic organophosphate pesticides have been replaced.<sup>2</sup> Although pyrethroids are less toxic than organophosphates to mammals and birds, detrimental effects have been associated with pyrethroid containing products.

Pyrethroids have been implicated as reproductive toxicants in humans and several species of animals. The effects of pyrethroids on reproductive or endocrine function have been investigated in several studies using a variety of animals as well as humans. Results from these studies have shown or suggested that these chemicals or their metabolites may disrupt endocrine function<sup>3-11</sup> and affect semen quality.<sup>4,12-18</sup> Several studies in humans showed associations between pyrethroid metabolites and reduced sperm concentration, motility, and normal morphology.<sup>19-21</sup> Contamination of the environment with pyrethroids may also affect aquatic animal reproduction.<sup>22,23</sup>

One of the purported mechanisms for disruption of endocrine function by pesticides is through mimicking or blocking the actions of the steroid hormones via binding to hormone receptors.<sup>10</sup> These

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receptors play critical roles in the differentiation, development and maintenance of male reproductive functions. Liu et al demonstrated that permethrin and cypermethrin have anti-androgenic activity by interfering with the androgen receptor.<sup>18</sup> A significant decrease in numbers of androgen receptors and in sperm production was found in rats treated with high levels of beta-cypermethrin; however, no changes were seen in the reproductive organs.<sup>18</sup> *In vitro* studies have been conducted using rat and cattle ovarian tissues and cells to assess effects of pyrethrins on reproduction.<sup>11,24</sup> In one study, treating luteal cells in culture with cypermethrin altered the production of progesterone and was toxic within 24 hours.<sup>11</sup> Several pyrethroids have also been reported to cause a decrease in testosterone production in male laboratory animals.<sup>4,13</sup>

Anecdotal evidence incriminating pyrethroids as a cause for decreased fertility in bulls and rams has been reported.<sup>25</sup> This report suggested that premise sprays and insecticide pour-ons may alter sperm motility and cause abnormal sperm morphology; however no controlled experiments were conducted. The implication that a commonly used insecticide may decrease productivity in animal agriculture is of high economic importance and interest to food animal industries.

The goal of this study was to determine if the commercially available synthetic pyrethroid, cyfluthrin, used in single or combined applications would negatively affect reproductive parameters in cattle. The specific objectives were to determine the effects of cyfluthrin, a commercially available pyrethroid product used according to label instructions on 1) sperm motility and morphology and serum testosterone concentrations in bulls and 2) serum progesterone concentrations and pregnancy rates in cows.

## Materials and methods

The products used in this study were a synthetic pyrethroid pour-on (cyfluthrin; CyLence®, Bayer Animal Health, Shawnee Mission, KS) and fly tag (beta-cyfluthrin; CyLence Ultra® insecticide cattle ear tag, Bayer Animal Health). All products were applied according to label directions and approved for use in food-producing animals. The fly tags also contain a synergist, piperonyl butoxide, which acts to enhance the pyrethroid properties but has no pesticidal effects.

### Experiment one

Angus x Simmental bulls (n=28) ranging from one to six years of age (BW=773.00±185.51 kg) were blocked by age and randomly assigned to one of four treatment groups. All bulls were owned by the University of Illinois and had no opportunity for sexual activity for at least one month prior to the experiment. Treatment groups consisted of: controls (CON, n=5) that received no pesticides; Pour-On (POUR, n=5) that received 24 mL of cyfluthrin liquid applied along the topline; Ear-Tag (TAG, n=7) that received an ear tag impregnated with beta-cyfluthrin in each ear; and a Pour-On/Ear-Tag (POUR + TAG, n= 7) that received both treatments applied at the same time. All animals were housed in non-adjacent pastures with their cohorts to prevent cross-contamination of products from animal to animal. Experiments were conducted from May through July. All bulls were maintained on endophyte infected tall fescue (*Festuca arundinacea*), red clover (*Trifolium pratense*), and white clover (*Trifolium repens*) pastures.

An initial physical examination including weight and body condition scoring was performed on each bull to establish health status. A reproductive examination was also performed to assess reproductive soundness prior to the experiment. Scrotal circumference was measured using scrotal tape. Tone and symmetry of each testicle and epididymis was assessed. Accessory sex glands were assessed through transrectal palpation. An electroejaculator was inserted into the rectum and a pre-programmed cycle was used to obtain a semen sample. Three or more mL of semen were collected from each bull. The penis was examined for abnormalities during the semen collection. Semen was collected by electroejaculation once each week for the following nine weeks within the same 4.5 hours of the day to negate diurnal effects on hormonal fluctuations. Semen was collected into 15 mL conical tubes using collecting handles and sleeves. Immediately after collection, the tube containing semen was transported in a warm (37°C) water bath to the laboratory. Semen was diluted 1:60 in saline (37°C) and 20 µL of

diluted semen was placed into a 20  $\mu$ L chamber slide (Vitrolife, Microcell Counting Chambers, San Diego, CA). Computer assisted sperm analysis (CASA) (Spermvision<sup>®</sup>, MiniTube of America, Inc., Verona, WI) was used to measure overall and progressive motility by averaging seven readings from various portions of the chambered slide. Morphological abnormalities were assessed by examining high power images (100X with phase contrast lens) of multiple sections of the chambered slide. Images were used to classify morphology as normal or abnormal. Abnormalities were further defined as primary or secondary by the same observer for all samples on all collection days. Following assessment of 100 sperm from each diluted semen sample the percentages of normal, primary, and secondary abnormalities were tabulated.

Blood was obtained for testosterone analysis prior to each weekly electroejaculation. Samples were obtained from the tail vein through a one inch 18 gauge needle into a serum-separating evacuated tube. Serum was removed after centrifugation 1200 rpm for 15 minutes with a sterile pipette and frozen at -20°C for later analysis. Testosterone concentrations were determined by double-antibody radioimmunoassay (Coat-A-Count<sup>®</sup>; Diagnostics Products Corporation, Los Angeles, CA) at the Animal Health Diagnostic Center, Cornell University, Ithaca, NY.

#### Statistical analysis

The experiment was conducted in a completely randomized design. Data were analyzed via the MIXED procedure of SAS (SAS Institute; Cary, NC). Repeated measures were used to analyze overall motility, progressive motility, normal morphology, and testosterone concentration using the covariate structure for compound symmetry. Individual bull was the experimental unit. Significance was declared at  $p \leq 0.05$ .

#### Experiment two

Mature, reproductively sound Angus and crossbred cows (n=123) were blocked by breeding date (April and July) and by breed, and randomly assigned to a control (CON; n=61) or pyrethroid group (POUR+TAG; n=62). All cows were owned by the University of Illinois, had a previous history of calving, and were in good body condition (4-6/9 BCS). The POUR + TAG group received both pour-on and fly tag cyfluthrin products at label doses. Insecticide was applied to the POUR+TAG group at the time of CIDR insertion. Cows were synchronized with a seven day CO-Synch+CIDR program.<sup>26</sup> Briefly, the CO-Synch+CIDR program is comprised of a 100 mcg dose of gonadotropin releasing hormone (GnRH; Cystorelin<sup>®</sup>, Merial, Duluth, GA) and a CIDR (Eazi-Breed<sup>™</sup> CIDR<sup>®</sup>, Zoetis, Florham Park, NJ) insertion on Day 0, followed by a seven day waiting period at which time the CIDR is removed and the cow is treated with a 25 mg of prostaglandin F<sub>2</sub>alpha (PGF; Lutalyse<sup>®</sup>, Zoetis). Cows were bred with semen of good quality by timed AI at 66-72 hours from CIDR removal by the same technician. Pregnancy was evaluated by transrectal palpation in combination with real-time ultrasound at Day 35 after AI.

Blood was obtained on days 10 and 17 after AI for measurement of progesterone concentrations. Samples were obtained from the tail vein through a one inch 18 gauge needle into a serum-separating evacuated tube. Serum was removed with a sterile pipette after centrifugation 1200 rpm for 15 minutes and the sample was frozen at -20°C. Concentrations of progesterone in the serum were determined by double-antibody radioimmunoassay (Coat-A-Count<sup>®</sup> kit; Diagnostics Products Corporation) at the Animal Health Diagnostic Center, Cornell University.

#### Statistical analysis

The experimental design was a randomized complete block. Treatments were randomly assigned to cows within blocks. Individual cow was the experimental unit. Non-categorical data were analyzed using the MIXED procedure of SAS. Categorical data were analyzed using the GENMOD procedure of SAS. Significance was declared at  $p \leq 0.05$ .

## Results

### Experiment One

Four bulls (two CON and two POUR) were excluded from the study due to medical conditions that required systemic antibiotic therapy. Individual bull weights and body condition scores remained consistent throughout the experimental period. Individual scrotal circumference measurements and assessment of accessory sex glands were also consistent throughout the experiment.

There were no treatment by time interactions for variation in motility or morphology (motility  $p=0.13$ ; morphology  $p=0.67$ ). The overall means for each treatment group across time were compared (Table 1). There were no differences in overall motility ( $p=0.41$ ; Figure), progressive motility ( $p=0.60$ ) or in percent normal morphology ( $p=0.41$ ) among treatments. Serum samples for testosterone measurement were lost from one bull in the CON group. Testosterone concentrations did not differ ( $p=0.16$ ) between CON and POUR + TAG bulls.

Table 1. Results of experiment one. Least square means of overall motility, progressive motility, normal morphology, and testosterone concentration in serum of bulls. CON=control; POUR=pour-on cyfluthrin product; TAG=ear tags impregnated with cyfluthrin; POUR+TAG=pour-on and ear tag cyfluthrin products; SEM=standard error of means.

Treatment Group	CON (n=5)	POUR (n=5)	TAG (n=7)	POUR+TAG (n=7)	SEM	P value
Observation						
Overall motility (%)	81.67	80.54	84.75	86.01	2.81	0.41
Progressive motility (%)	67.35	67.50	72.40	72.63	3.99	0.60
Normal morphology (%)	80.96	80.12	80.04	71.27	5.23	0.41
Testosterone (ng/ml)	8.17 (n=4)			14.35	3.22	0.16

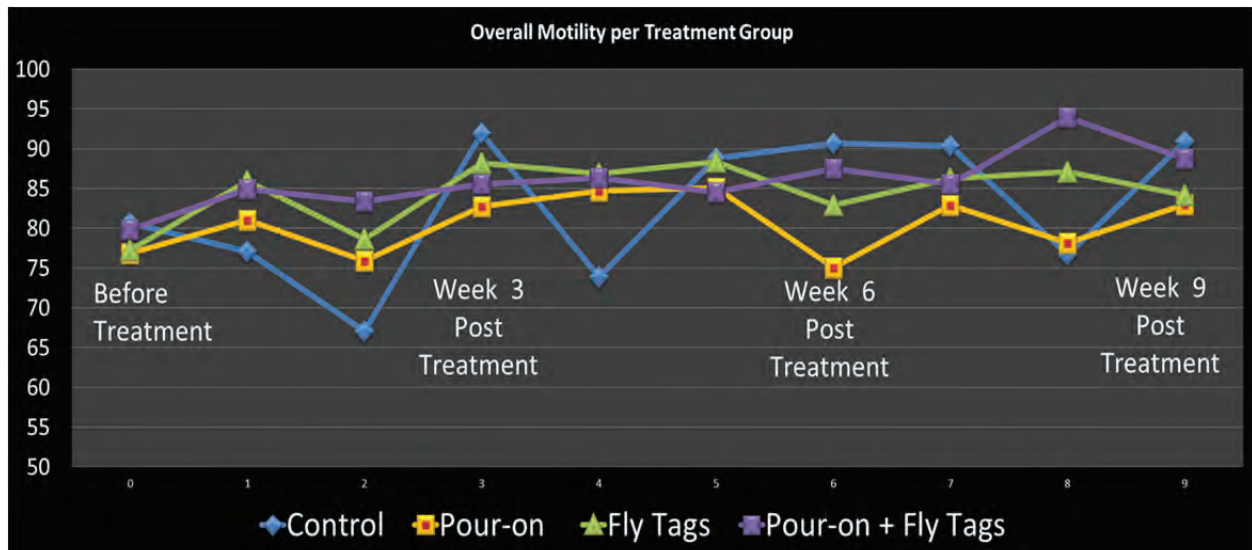


Figure. Scatterplot of means of overall motility for all treatment groups. No statistical differences ( $p=0.41$ ) were found between treatment groups.

### Experiment two

A significant difference in serum concentrations of progesterone was observed on day 10 but not on day 17 (Table 2). No differences ( $p=0.65$ ) were observed in AI pregnancy rates between POUR+TAG (45%) and CON (40%) cows.

Table 2. Results of experiment two. Mean concentrations of progesterone in serum at Day 10 and Day 17 and pregnancy rates in CON and POUR+TAG cows. CON=control; POUR+TAG=pour-on and ear tag cyfluthrin products; SEM=standard error of means.

Item	CON (n=61)	POUR+TAG (n=62)	SEM	P value
Day 10 progesterone (ng/ml)	6.4	5.5	0.3	0.02
Day 17 progesterone (ng/ml)	6.2	6.5	0.4	0.57
AI pregnancy rate	40%	45%	0.3	0.65

## Discussion

### Experiment one

According to previous reports of the effects of pyrethroids on bull and ram fertility, a decrease in motility would be expected to result quickly after exposure to the pesticide.<sup>25</sup> Semen collections were performed weekly for nine weeks in order to account for early variation in motility and long-term variation in morphology. No treatment by time effects were detected throughout the experiment and no significant differences were noted in motility parameters. Morphology was monitored weekly for 62 days to span the period of time necessary for completion of one spermatogenic cycle. No significant differences in morphologies were detected across all treatment groups for the duration of the experiment.

The route of exposure could play a critical role in the amount of pyrethroid the animals absorb. A study using rats compared absorption of orally and dermally administered pyrethroids and found 75% of orally applied pyrethroids were absorbed compared to 20% following topical administration.<sup>27</sup> Another study in humans found absorption of 35% after an oral dose of permethrin compared to 2% after dermal application.<sup>28</sup> Limited residues of cyfluthrin were detected in whole blood and liver, and slight residues were detected in fat, muscle, kidney, and whole milk following dermal applications suggesting a low level of absorption transdermally.<sup>29</sup> Concentrations of cyfluthrin in the serum were not determined in the current study.

Results from animal experiments with male New Zealand White rabbits showed that oral treatment with cypermethrin resulted in a significant decrease in ejaculate volume, sperm concentration, total sperm output, sperm motility, total motile sperm per ejaculate, and packed sperm volume.<sup>13</sup> In a study of 30 Sprague-Dawley rats treated orally with 30 mg/kg of beta-cypermethrin for 15 days, a negative effect was seen in daily sperm production.<sup>18</sup> In contrast, 135 Wistar rats treated with 40 mg/kg doses of oral fenvalerate exhibited no detrimental effects in reproductive parameters.<sup>16</sup> In experiments conducted on dwarf goats, the entire animal was dipped in varying percentages of cypermethrin at Day 0 and Day 15. A dose-dependent decline in semen quality was observed at Day 30, however, semen quality returned to normal by Day 75.<sup>17</sup> Results from these experiments suggest that decreases in fertility associated with pyrethroids may be dependent on type of pyrethroid, dosage, and route of exposure. The dosages used in many of these studies were commonly twice the recommended dosages and oral routes of administration were most commonly used. Volkmann's report on the effects of pyrethroids on bull and ram infertility involved a premise spray (bifenthrin) that could have saturated the entire environment, including water and feed containers. The current study found no effects on bull fertility when cyfluthrin was applied topically and at the labeled dose. Animals were grouped in pastures based on their treatment groups and may have had the opportunity to ingest the product from a pasture-mate's back. No detrimental effects were seen in this experiment, but animals in a more confined housing system may have the opportunity to ingest more product.

Pyrethroids have been reported to have antiandrogenic activity and may inhibit hormone production.<sup>3-11</sup> Testosterone concentrations were analyzed for the CON and POUR+TAG treatment groups in this experiment and no significant differences were found. Arena et al conducted experiments on rats using fenvalerate and found similar results with no changes in testosterone concentrations.<sup>16</sup> In contrast, Zhang et al found that oral administration of cis-permethrin (35 and 70 mg/kg) for 42 consecutive days in mice decreased testosterone concentrations.<sup>4</sup> Oral permethrin also decreased testosterone concentrations in rabbits after 16 weeks of administration.<sup>13</sup> In experiments assessing

hormone receptor activity, Du et al<sup>10</sup> found the relative potency of antagonistic activities descended in the following order: deltamethrin > cyfluthrin > fenvalerate > cyhalothrin > cypermethrin > permethrin > 3-phenoxybenzoic acid. They also reported that antiandrogenic activities of deltamethrin and cyfluthrin were more potent than other compounds.<sup>10</sup> Differences in the concentrations of testosterone as reported by other investigators, like changes reported for motility and morphology, may be dependent on the type of pyrethroid used, the route of administration, and dose.

#### Experiment two

Several studies have suggested that pyrethroid products had toxic effects on cells of the corpus luteum which could alter the production of progesterone.<sup>5,11,24</sup> In this study, progesterone was measured in serum collected on Day 10 after AI when the ovaries of all cows (CON and POUR+TAG) should have contained a functional corpus luteum regardless of their pregnancy status. Progesterone analysis was also performed on Day 17 after AI. As there were no differences in the rates of pregnancy between the two treatment groups, comparison of concentrations of progesterone at Day 17 between pregnant and non-pregnant cows within each group was not pursued.

Cows in the POUR+TAG group had significantly lower concentrations of progesterone in their serum at Day 10, but this difference was not seen at Day 17. Fei et al reported that the pyrethroid, fenvalerate, had concentration-related inhibitory effects on follicular growth characterized by low granulosa cell numbers with no significant effects on follicular survival rates.<sup>30</sup> It is possible that pyrethroids used on the cows in the present study affected pre-ovulatory follicles, initially inhibiting cells that would later be responsible for progesterone production, but this inhibition could be overcome by Day 17. Another study using bovine luteal cells *in vitro* indicated that cypermethrin caused a transient decrease in progesterone production.<sup>11</sup> If pyrethroid application similarly affected luteal cells in our study at Day 10, the effect may have been overcome by Day 17. The findings from this experiment suggest that pour-on and ear tags can have an early, time-dependent effect on serum progesterone concentrations. Elucidating the absorption of cyfluthrin, the exposure to specific bovine ovarian tissues, and the possible mechanisms for decreased concentrations of progesterone will require additional experiments.

Results from experiments conducted on pregnant rats receiving oral administration of a synthetic pyrethroid, deltamethrin, indicated that a sublethal dose could produce qualitative and quantitative alterations in the blastocyst-endometrium interaction, compromising the implantation process.<sup>24</sup> The results from the current study indicated no significant difference in conception rates between cows in the CON and POUR-TAG treatment groups

#### Conclusion

Cyfluthrin pyrethroid insecticide ear tags and pour-on products did not result in negative effects on the male or female cattle reproductive parameters measured. A transient effect on the concentration of progesterone in the serum of cows was not associated with decreased pregnancy rates.

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