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Received: 21 June 2023 | Revised: 22 August 2023 | Accepted: 12 September 2023

DOI: 10.1111/jvp.13409

JOURNAL OF Veterinary Pharmacology and Therapeutics WILEY

ORIGINAL ARTICLE

Depletion of dexamethasone in cattle: Food safety study in dairy and beef cattle

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Funding information
Beef Farmers of Ontario; Dairy Farmers of Ontario; Ontario Ministry of Agriculture, Food and Rural Affairs

Abstract

Dexamethasone is approved for cattle in Canada for several conditions, but no withdrawal times are currently provided on the approved labels. Recently, the list of Maximum Residues Limits for Veterinary Drugs in Foods in Canada was amended to include dexamethasone. The objectives of this study were to determine the residue depletion profile of dexamethasone after an extra-label dosage regimen in milk of healthy lactating dairy cattle ($n = 18$) and in edible tissues of healthy beef cattle ($n = 16$) and to suggest withdrawal intervals. Dexamethasone was administered intramuscularly at 0.05 mg/kg daily for 3 days. Milk samples were collected prior to treatment and every 12 h up to 96 h post-dose. Muscle, liver, kidney, and peri-renal fat tissues were collected from beef cattle at 3, 7, 11, or 15 days post-dose. Dexamethasone analysis was performed by liquid chromatography/mass spectrophotometry. Dexamethasone residues were detected in milk samples up to 36 h. Muscle and fat had no detectable dexamethasone residues while kidney and liver had detectable residues only on day 3 post-dose. A withdrawal interval of 48 h for milk in Canadian dairy cattle and 7 days for meat in Canadian beef cattle are suggested for the dexamethasone treatment regimen most commonly requested to CgFARAD™.

KEYWORDS
cattle, depletion, dexamethasone, extra-label, withdrawal intervals

1 | INTRODUCTION

Dexamethasone is a synthetic glucocorticoid approved in Canada and the United States (US) in both dairy and beef cattle for a variety of veterinary therapeutic uses, including inflammatory conditions and parturient udder edema. It is also approved for the treatment of bovine ketosis, but benefits are small and conditional (Tatone et al., 2016). Currently in Canada, dexamethasone is approved as an oral powder or injectable solution supplied by multiple pharmaceutical companies. Approved labels have varying dosage regimens for dexamethasone sodium phosphate injectable products ranging from 0.044 mg/kg daily IM or IV to 5–20 mg per animal IM or IV. Dexamethasone is also used extra-label at varying dosage regimens in Canada and the US. Despite the common use of dexamethasone and its widespread availability, product labels in Canada and the US do not provide withdrawal times for meat or milk, which may be misinterpreted by product users as a "zero withdrawal time". The European Union's (EU) maximum residue limits (MRLs)

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for dexamethasone in cattle are 2 ppb for liver, 0.75 ppb for muscle, 0.75 ppb for kidney, and 0.3 ppb (μg/L or ng/mL) for milk (The European Commission, 2010), while the CODEX Alimentarius MRLs are 2 ppb for liver, 1 ppb for muscle, 1 ppb for kidney, and 0.3 ppb for milk (Codex Alimentarius, 2022). Recently, the list of MRLs for Veterinary Drugs in Foods in Canada was amended to include dexamethasone at 1 ppb for muscle and kidney, 2 ppb for liver, and 0.3 ppb for milk (https://www.canada.ca/en/health-canada/programs/consultation-proposal-maximum-residue-limits-veterinary-drugs-foods-mrl-2023-1/document.html). Currently, there are no legal tolerances in the US for dexamethasone in tissues or milk of cattle. In 2012, the US Food Safety and Inspection Service instituted Multi-Residue Methods (MRM) that included dexamethasone, and subsequently detected dexamethasone tissue residue violations in cattle. Discussions with stakeholders and reviews of the US Food and Drug Administration approval documentation led to the conclusion that there was no basis for a food safety concern with dexamethasone, due to rapid elimination and low risk to human health. Dexamethasone was therefore removed from the US National Residue Program (The Pew Charitable Trusts, 2016). US veterinarians and producers were able to return to using zero days for the withdrawal time for dexamethasone products with no withdrawal time on the label, as long as the drug was used as labeled. The Canadian Food Inspection Agency also uses sensitive MRM including dexamethasone, and no dispensation has been granted for detection of dexamethasone residues in Canadian cattle. Highlighting this, Ontario data provided by the Ontario Ministry of Agriculture, Food and Rural Affairs reports (Troy Jenner, Manager, Food Safety Science Unit, OMAFRA) since May 2019 in Ontario-licensed abattoirs there has been a dexamethasone violation rate of approximately 1.11% in cattle carcasses (steers, cull dairy cows, heifers, and male veal calves) selected for residue testing through monitoring and surveillance programs, with steers and cull dairy cow making up the majority of test positives. This suggests that the presumed zero withdrawal time followed by Canadian producers results in detectable dexamethasone residues at slaughter.

Previous depletion studies in milk suggested a withdrawal period of 72 h after IM dexamethasone injection (Caloni et al., 2000; Fairclough et al., 1981). However, these studies had low animal numbers per study groups and employed less sensitive and/or specific analytical methods (enzyme immunoassay and radioimmunoassay) than liquid chromatography/mass spectrophotometry (LC–MS) assays used by regulatory authorities. With respect to tissue residues in cattle, only two studies could be found. In the first study, three milk-fed calves were administered short acting sodium phosphate ester in combination with the long-acting phenylpropionate ester of dexamethasone and they were slaughtered 24 h after IM injection (Van Den Hauwe et al., 2003). Using an immunoassay, dexamethasone residues ranged from 4.1 to 32.8 ppb in liver, 0.8 to 4.5 ppb in muscle, and 2.4 to 15.0 ppb in kidney. The second study used 10 calves that received an oral formulation of dexamethasone for 20 days and 10 calves that received dexamethasone 21-disodium phosphate 2 mg/kg of IM q 12 h for 3 days. Both groups were slaughtered 30 days after the last dose (Ferranti et al., 2013). Tissue samples analyzed by liquid LC-MS measured dexamethasone residues at concentrations of 0.4–1.0 ppb in liver, 0.4–0.6 ppb in kidney, and 0.2–0.6 ppb in muscle. All tissue concentrations were below the respective EU, CODEX, and Canadian MRL values. From two studies with only single slaughter time points, it is impossible to predict a depletion profile for dexamethasone-treated cattle.

The CgFARAD™ (www.cgfarad.usask.ca) is a Canadian service providing expert-mediated veterinary pharmacology advice for residue avoidance to veterinarians. Since its beginning in 2002, the service has received numerous requests for withdrawal advice in lactating dairy cattle and beef cattle for both on label and extra-label use of injectable dexamethasone prescribed by licensed Canadian veterinarians. A search of the CgFARAD™ database records revealed the most common uses for dexamethasone that resulted in requests to the CgFARAD™ were for analgesia and anti-inflammatory activity (mainly associated with calving trauma), followed by adjunct treatment of atypical interstitial pneumonia and other respiratory conditions, induction of abortion, and treatment of ketosis (dairy cattle). The CgFARAD™ has provided conservative withdrawal recommendations of 10 days for meat and 96 h for milk for most on label uses of injectable dexamethasone, with extended extra-label withdrawal recommendations depending on dosage regimens used and the condition being treated. The most common dosing regimen requested to the CgFARAD™ for withdrawal recommendations in both lactating dairy cattle and beef cattle is 0.05 mg/kg IM once daily for three consecutive days.

The objectives of this study were to determine the residue depletion profile of dexamethasone after an extra-label dosage regimen in milk of lactating dairy cows in order to suggest a suitable milk withdrawal interval, and in edible tissues of beef cattle in order to suggest a suitable meat withdrawal interval.

2 | MATERIALS AND METHODS

Both depletion studies were conducted at the University of Guelph research facilities in Elora, Ontario with the dairy cattle study conducted at the Ontario Dairy Research Centre and the beef cattle study at the Ontario Beef Research Centre. The studies were conducted according to recommendations provided by VICH GL 48, whose guidelines are utilized by the Veterinary Drugs Directorate at Health Canada and the Center for Veterinary Medicine at the US FDA for veterinary drug approvals (VICH, 2015). Both studies animal use protocols were approved by the University of Guelph Animal Care Committee (AUP #4441).

2.1 | Dexamethasone depletion in milk of lactating dairy cattle

Following a 10 day acclimation period, 20 lactating dairy cattle were enrolled in this study. Cattle were at least 2 years of age and at varying stages of their lactation cycles (e.g., early – 1–100 days, mid – 101–200 days, and late lactation – 201–300 days) in order to include

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high and low milk-yielding animals. All animals were in good health and had negative California Mastitis Test result at the start of the study as determined by a veterinarian. All animals were given an IM injection of dexamethasone sodium phosphate (Dexamethasone 5, Vetoquinol) at 0.05 mg/kg in alternating sides of the neck once daily for 3 days. Two 50 mL composite milk samples (from all four quarters) were collected prior to dexamethasone administration and at 12, 24, 36, 48, 60,72, 84, and 96 h after the last dose. All other milk collected during the study period was discarded and not used for human consumption. All cows were milked on a twice daily schedule according to standard industry practices and each cow was completely milked out after each sample collection. All collected samples were frozen (−80°C) until assayed for dexamethasone by the Agriculture and Food Laboratory (AFL) at the University of Guelph using a validated mass spectrometry assay. Additional control whole milk samples were collected from several cows prior to dosing with dexamethasone for validation of the liquid chromatography/mass spectrophotometry dexamethasone assay.

2.2 | Dexamethasone depletion in edible tissues of beef cattle

Following a 14 day acclimation period, four animals (two steers; two heifers) were randomly allocated to one of four slaughter time points (3, 7, 11, or 15 days after the last dexamethasone administration) for a total of 16 animals in the study. Two healthy untreated beef cattle (steer and heifer) were slaughtered for collection of control tissues (muscle, liver, kidney, and peri-renal fat) for mass spectrometry assay validation. All cattle were between 275 and 325 kg (~6 months of age) at the start of the study and in good health based on physical examination by a veterinarian. Cattle were administered monensin in the feed during the study for coccidiosis control. All animals were given an IM injection of dexamethasone sodium phosphate at 0.05 mg/kg in alternating sides of the neck once daily for 3 days. On the day of sacrifice, animals were transported to the University of Guelph Meat Laboratory and sacrificed by stunning and exsanguination followed by collection of muscle, liver, kidney, and fat samples. Samples were collected in duplicate in 50 mL sample tubes, then frozen (−80°C) until assayed for dexamethasone by the AFL at the University of Guelph using a validated liquid chromatography/mass spectrophotometry assay. All remains of the cattle used in the study were incinerated for disposal and did not enter any food chain.

2.3 | Quantitation of dexamethasone in bovine milk and tissues using LC MS/MS

The LC MS/MS quantitation of dexamethasone was conducted by the AFL at the University of Guelph, Guelph, Ontario, Canada. Reference standard dexamethasone was purchased from Toronto Research Chemicals (Toronto, ON, Canada) and its deuterated internal standard dexamethasone – d4 (IS) was from CDN Isotopes Inc. Ultrapure Optima grade of acetonitrile, methanol, hexane, formic acid, and water were from Fisher Scientific. Dexamethasone and its internal standard stock solutions were prepared in methanol and stored at −80°C.

To extract dexamethasone from fat, muscle, kidney, and liver, a 10 µL aliquot of the dexamethasone—d4 (IS) solution was spiked to a 1 g ± 0.01 g of finely chopped tissue sample, and 10 mL of extraction solution (ACN:H_2O, 90:10 v:v) was added. For milk samples, a 10 µL aliquot of the IS solution was spiked to a 1 mL raw milk sample, and 9 mL of extraction solution was added. The tissue samples were homogenized using a Geno/Grinder 2010 (SPEX SamplePrep) for 30 s at 1350 oscillations/min, and then centrifuged at 7200 *g* for 10 min at 4°C. An 8 mL aliquot of supernatant was mixed with 4 mL hexane and homogenized again using a Geno/Grinder for 30 s at 1350 oscillations/min. After centrifugation at 7200 *g* for 2 min, the hexane layer was removed and the acetonitrile layer was evaporated to approximately 200 µL using a turbovap at 65°C under nitrogen gas (18 psi). The extraction tube was rinsed with another 250 µL of acetonitrile, then 550 µL of water was added. The combined 1 mL of acetonitrile/water solution was centrifuged at 30,130 *g* for 30 min at 4°C. The supernatant was transferred to an injection vial for LC MS/MS analysis. Calibration curves for each tissue matrix were prepared fresh on the day of analysis by spiking working standard solutions into blank tissue samples.

A Shimadzu Nexera UHPLC system (Tokyo, Japan) was used for LC analysis. Separations were achieved on a Waters ACQUITY UPLC CSH C18 column (1.7 µm, 2.1 × 30 mm) with column temperature maintained at 35°C. Mobile phase A consisted of 0.1% formic acid in water and methanol (99.5:0.5, v/v), and mobile phase B was methanol with 0.1% formic acid. The gradient conditions were set as follows: from 0 to 3.5 min ramp from 0% to 100% of mobile phase B, maintain 100% B for 3 min, then ramp back to 0% B. The flow rate was 0.5 mL/min and 1 µL of sample was injected on to the column. Retention time for dexamethasone was 4.4 min with a total run time of 9 min.

Positive electrospray ionization (ESI) mass spectrometry analysis was operated in multiple reaction monitoring (MRM) mode using a Sciex Triple Quad 5500 mass spectrometer (Concord, ON, Canada). The instrument was equipped with a Turbo V source and electrospray probe with desolvation gas temperature set at 610°C. The source conditions were optimized as: IonSpray voltage (IS) 5000 V, collision gas 8, curtain gas 25, GS 1 20, and GS 2 50. Data were acquired and processed using Analyst 1.7.1 (SCIEX AB). For quantitation, MRM transitions were monitored at *m/z* 393.2→373.1 as target ion and 393.2→147.1 as qualifier ion for dexamethasone, and 397.4→359.3 for dexamethasone-d4 (IS), all with collision energy (CE) of 15 V.

The LC MS/MS method was validated including linearity, sensitivity, precision, and accuracy. Based on three times signal to noise ratio. The limits of detection (LOD) were 0.05 ppb for milk, 0.6 ppb for liver, and 0.7 ppb for fat, muscle, and kidney tissues. The limits of quantification (LOQ) were 0.15 ppb for milk, 2 ppb for muscle, kidney, and liver and 3 ppb for fat based on the lowest concentration of the validated reference curves. Calibration standards and

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quality controls were prepared and assayed on two separate days for fat, muscle, kidney, and liver tissues, and six separate days for milk samples. Five-point calibration curves were generated for each sample matrix at the following concentration ranges: 0.15–20 ppb for milk samples, 3–40 ppb for fat, and 2–40 ppb for muscle, kidney, and liver tissues. All calibration curves were linear with a coefficient of determination (R^2) > 0.99. For five sample matrices, the accuracies were within 15% of the nominal concentration for all calibration levels, except for the LOQ, which was within 20%. The intra- and inter-day precision values were all within 15% (CV).

2.4 | Statistical analysis

Comparisons of dexamethasone residue concentrations in milk by lactation stage were performed using one-way analysis of variance (Graphpad Prism 9.3.1). Milk residue depletion modeling was performed using an open access Microsoft Excel-based workbook for statistical evaluation of veterinary drug residue depletion data produced for the Joint FAO/WHO Expert Committee on Food Additives (JECFA; Joint FAO/WHO Expert Committee on Food Additives, 2006). Four regression lines were calculated from the dexamethasone residue concentrations over time in milk: exponential regression of the actual residue data (commonly referred to as median residues) and three upper tolerance limits (UTLs): the one-sided 95% confidence interval over the 95th percentile of residue concentrations (95/95 UTL), one-sided 95% confidence interval over the 99th percentile of residue concentrations (99/95 URL), and one-sided 99% confidence interval over the 99th percentile of residue concentrations (99/99 UTL, not shown).

3 | RESULTS

Although 20 cows were enrolled in the study, dexamethasone residue data in milk from 18 cows was included for analysis. One cow sustained a musculoskeletal injury during the study requiring treatment with another anti-inflammatory (meloxicam) and was removed from the study. Milk from another cow had quantifiable dexamethasone residues in the pre-dose milking sample believed due to a sample mix up, thus her subsequent milk samples were excluded from analysis. Of the 18 remaining cows, seven were in early lactation, four were mid-lactation, and seven were late lactation.

Dexamethasone residues were quantifiable (≥0.15 ppb) in milk samples from all remaining18 cows from the first two milkings post-dose (12 and 24 h) and in 17/18 milk samples at the third milking (36 h). The remaining milk sample at 36 h contained detectable (>5 ppb) but sub-quantifiable dexamethasone, for which the statistical program assigned a value of ½ LOQ (7.5 ppb). Dexamethasone residues were not detectable in milk samples from any animal at ≥48 h post-dose, therefore, only the 12, 24, and 36 h milk samples were included in the statistical analysis of residues. Mean dexamethasone residue concentrations for the first three milkings are shown in Table 1. At each milking time, there were no statistically significant differences in mean dexamethasone concentrations between lactation stages.

The exponential regression of milk residue concentrations (median residues) and 95/95 and 99/95 UTLs are shown in Figure 1. All statistical assumptions underlying the regression of the analysis of variance were met (Bartlett's test for equality of variances across groups, Cochrane C test for variance outliers).

The elimination rate constant (k_{el}) for dexamethasone residues in milk was 0.103 h^{-1}, resulting in a milk elimination half-life of 6.7 h ($T_{1/2\ elim} = \ln 2/k_{el}$). The projected times required for median, 95/95 UTL, and 99/95 dexamethasone residues in milk to reach EU/CODEX/Canadian MRL of 0.3 ppb are 32, 38, and 41 h, respectively. Residues reach the assay LLOQ (0.15 ppb) in 39 h (median) – 47 h (99/95 UTL), and assay LOD (0.05 ppb) in 50 h (median) – 58 h (99.95 UTL; Table 2).

Dexamethasone rapidly depleted from bovine tissues. Kidney and liver residues were only quantifiable on day 3 post-dosing (Table 3). Dexamethasone residues in muscle and fat were not detectable in tissue samples any time point.

4 | DISCUSSION

Prior to this study, only limited depletion information was available to the CgFARAD™ for determining withdrawal recommendations for meat and milk of cattle treated with dexamethasone

TABLE 1 Comparisons of dexamethasone residues (parts per billion) in milk samples obtained from 18 healthy lactating dairy cows at early, mid, and late lactation after daily intramuscular administration of dexamethasone sodium phosphate at 0.05 mg/kg for 3 days.

Withdrawal time	All animals ($n = 18$)	Early lactation ($n = 7$)	Mid lactation ($n = 4$)	Late lactation ($n = 7$)	p-Value[a]
12 h	2.61 ± 0.61	2.82 ± 0.58	2.50 ± 0.11	2.46 ± 0.79	.52
24 h	0.70 ± 0.21	0.80 ± 0.24	0.65 ± 0.11	0.62 ± 0.79	.24
36 h	0.23 ± 0.08	0.25 ± 0.10	0.21 ± 0.05	0.21 ± 0.07	.63
≥48 h	BLOD				

Note: Data expressed as Mean ± SD.

Abbreviations: h, hours; *n*, number of animals. BLOD: All samples taken from 48 to 96 h after the final injection were below the assay limit of detection (0.05 ppb).

[a]Statistical analysis was performed using One-way ANOVA.

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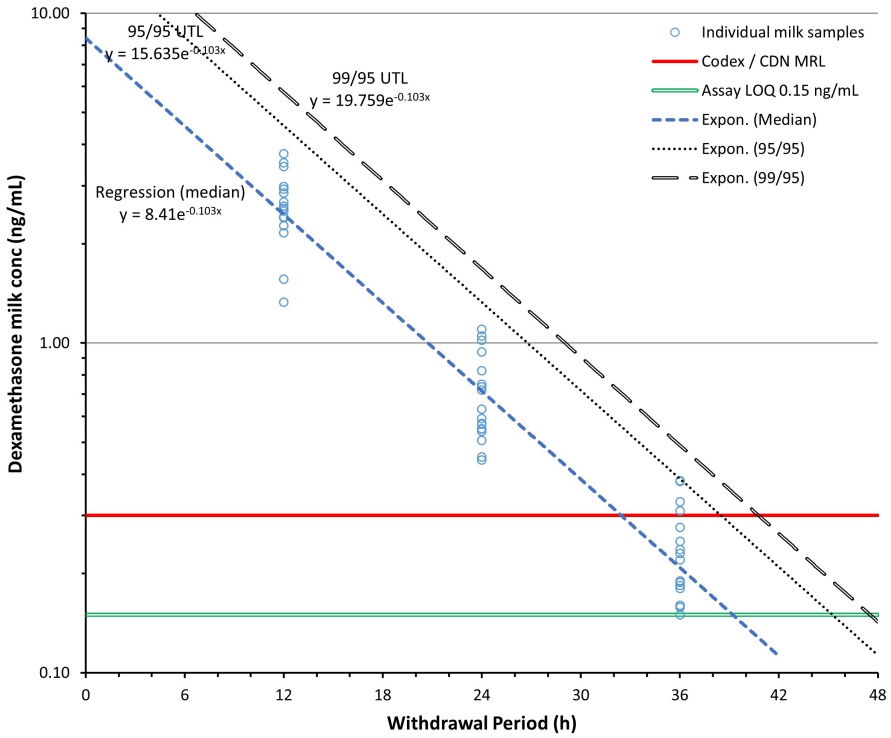

FIGURE 1 Milk dexamethasone concentration-time profile across sampling time points (12, 24, and 36 h) after daily intramuscular administration of dexamethasone sodium phosphate at 0.05 mg/kg for 3 days in 18 healthy lactating dairy cows.

TABLE 2 Time required for dexamethasone residues in milk to reach Codex proposed MRL, LLOQ or LOD after daily intramuscular administration of dexamethasone sodium phosphate at 0.05 mg/kg for 3 days in 18 healthy lactating dairy cows.

Residue target	Median residues	95/95 UTL	99/95 UTL
EU/Codex/Canadian MRL (0.3 ppb)	32.4 h	38.4 h	40.7 h
Assay LLOQ (0.15 ppb)	39.1 h	45.1 h	47.4 h
Assay LOD (0.05 ppb)	49.8 h	55.8	58.1

Abbreviations: h, hours; LLOQ, lower limit of quantification; MRL, maximum residue limit; ppb, parts per billion; UTL, upper tolerance limit.

sodium phosphate. Previous studies used different formulations and/or treatment regimens, less sensitive assays, and small animal numbers. Although widely used in human and veterinary medicine, there are concerns regarding the use of glucocorticoids in cattle (Cannizzo et al., 2011; Cantiello et al., 2009; Courtheyn et al., 2002; Girolami et al., 2010; Graham et al., 2012). In the original evaluations, no genotoxicity relevant to human health was observed, therefore, an acceptable daily intake (ADI) could be established for dexamethasone. In animal toxicology studies, major adverse effects of dexamethasone were a decrease in white blood cell counts (WBC), atrophy of the thymus and spleen, as well as the decrease in adrenal weights. These effects are to be expected from dexamethasone's glucocorticoid action. JECFA and EMEA determined an acceptable daily intake (ADI) of 0.015 µg/kg bw/day (up to 0.9 µg/60 kg person) based on the expected pharmacological actions, and the induction of tyrosine aminotransferase activity (TAT) in rat liver (The European Agency for the Evaluation of Medicinal Products, 1997). Dexamethasone and other synthetic

TABLE 3 Dexamethasone residue concentrations in edible tissues of beef cattle administered daily intramuscular injections of dexamethasone sodium phosphate at 0.05 mg/kg for 3 days.

Animal #	Withdrawal (days)	Concentration of dexamethasone (ppb)[a]			
		Liver	Kidneys	Muscle	Fat
	Control	ND	ND	ND	ND
4M	3	2.97	2.5	ND	ND
6M	3	5.84	4.3	ND	ND
11F	3	6.15	6.7	ND	ND
15F	3	5.20	5.3	ND	ND
8M	7	<LOQ	ND	ND	ND
9M	7	ND	ND	ND	ND
14F	7	ND	ND	ND	ND
18F	7	<LOQ	ND	ND	ND
1M	11	ND	ND	ND	ND
2M	11	ND	ND	ND	ND
16F	11	ND	ND	ND	ND
17F	11	ND	ND	ND	ND
5M	15	ND	ND	ND	ND
7M	15	ND	ND	ND	ND
12F	15	ND	ND	ND	ND
13F	15	ND	ND	ND	ND

Note: Values <LOQ, but >LOD are presented as <LOQ and not included in the computation of the means. ND = Not Detected at a Limit of Detection (LOD) concentration of 0.7 ppb (muscle, kidney) 0.6 ppb (liver) or 3 ppb (fat). Values <LOQ, but >LOD are presented as <LOQ and not included in the computation of the means.

[a]Limit of Quantitation (LOQ) = 2 ppb (muscle, kidney and liver) or 3 ppb (fat).

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glucocorticoids increase feed intake and promote weight gain or affect meat quality by increasing water content, and the EU considers them the most important of the illegal growth promoters and banned any extra-label use in 2003 (Ferranti et al., 2013). In addition, the detection of glucocorticoids serves as a marker for illicit β-agonist use, as they prevent β-receptor down-regulation and tolerance to drugs such as clenbuterol (Abraham et al., 2004; Courtheyn et al., 2002; Odore et al., 2007).

The extra-label dosage regimen for dexamethasone sodium phosphate of 0.05 mg/kg IM q 24 h for 3 days resulted in detectable residues of dexamethasone in both milk of lactating dairy cows and edible tissues of beef cattle. The concentrations of dexamethasone in milk at a zero withdrawal time, which is considered 12 h after drug administration (mean = 2.61 ppb), greatly exceeded EU/CODEX/Canadian MRL of 0.3 ppb. Minimal variance in dexamethasone milk residue concentrations was observed at each of the milk collection times. The ratio of lowest to highest dexamethasone residues in the 18 sets of milk samples analyzed was approximately three-fold at each of the first three milking. Concentrations ranged from 1.33–3.75 ppb (12 h), 0.44–1.11 ppb (24 h), and 0.11–0.38 ppb (36 h). Due to the minimal variance between dexamethasone milk residue concentrations at each milk collection time, as well as large sample size ($n = 18$ at each sample time point), there was relatively little spread between the regression lines calculated for the 95th and 99th percentiles of residues and the regression line for the observed milk residues (median regression). This is illustrated by the relatively small difference in time between the median, 95th, and 99th percentiles to reach the CODEX/Canadian MRL of 0.3 ppb or the assay LLOQ/LOD (Table 2). Based upon the milk residue data presented, a 48 h milk withdrawal period would be suitable for the dexamethasone treatment regimen commonly used in Canadian dairy cows, and in this study.

Dexamethasone residues depleted rapidly from tissues of treated beef cattle, with quantifiable tissue residues only present in liver and kidney samples on the first slaughter time point 3 days post-administration. Muscle and fat dexamethasone residues were not detected at any time point. Based upon the tissue residue data from this study, a 7 day withdrawal period would be suitable for the dexamethasone treatment regimen commonly used in Canadian beef cattle, and in this study.

Introduction of meat and milk withdrawal periods (and the ensuing economic costs) after dexamethasone administration in cattle could conceivably reduce dexamethasone usage in these animals. Drugs with shorter, or no withdrawal periods, could be used instead of dexamethasone for similar indications (e.g., ketoprofen for anti-inflammatory effect, oral or intravenous gluconeogenic agents for ketosis). More concerning would be situations in which no alternative therapy to dexamethasone is utilized, and the animal's condition remains untreated. However, CgFARAD™ records indicate that many dexamethasone-treated cattle have pathologic conditions being treated with other medications (e.g., antimicrobials), for which longer milk and meat withdrawal periods are usually required than proposed here for dexamethasone. Therefore, these recommendations should not have an adverse impact on dairy and beef cattle production practices.

AUTHOR CONTRIBUTIONS

Al Chicoine: data interpretation, statistical analysis, manuscript drafting; David L. Renaud: study design, data interpretation, manuscript drafting; Saad S. Enouri: drug administration, sample collection, data interpretation, manuscript drafting; Patricia M. Dowling: data interpretation, manuscript drafting; Yu Gu: manuscript drafting; Ron J. Johnson: study design, sample collection, data interpretation, manuscript drafting.

ACKNOWLEDGMENTS

The authors thank the Dairy Farmers of Ontario, Beef Farmers of Ontario, and the Ontario Ministry of Agriculture, Food, and Rural Affairs (OMAFRA) for their financial support for this study.

FUNDING INFORMATION

This study was funded by Dairy Farmers of Ontario, Beef Farmers of Ontario, and Ontario Ministry of Agriculture, Food, and Rural Affairs (OMAFRA).

CONFLICT OF INTEREST STATEMENT

We declare that we have no conflicts to disclose to our knowledge.

DATA AVAILABILITY STATEMENT

Data are available from the corresponding author upon reasonable request.

ANIMAL WELFARE AND ETHICS STATEMENT

The animal use protocols of this study were approved by the University of Guelph Animal Care Committee AUP #4441.

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How to cite this article: Chicoine, Al, Renaud, D. L., Enouri, S. S., Dowling, P. M., Gu, Yu, & Johnson, R. J. (2023). Depletion of dexamethasone in cattle: Food safety study in dairy and beef cattle. *Journal of Veterinary Pharmacology and Therapeutics*, *00*, 1–7. https://doi.org/10.1111/jvp.13409

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