



# Prevalence of Ivermectin Residues in Cattle Slaughtered in Federally Inspected Abattoirs in Nuevo Leon, Mexico

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## ABSTRACT

A study was performed in Nuevo Leon, a northern state of Mexico, to detect the presence of ivermectin residues in cattle slaughtered in federally inspected abattoirs, because of suspected increased use of ivermectin on farms. In a total of 234 liver samples taken during one month, ivermectin residue exceeding the Maximum Residue Level (MRL) was found in one sample (prevalence 0.004; 95% exact binomial confidence interval 0.0047 to 0.0432). These findings are consistent with those of the Mexican residue monitoring program in 2006–08. We stress the importance of further research to identify risk factors associated with non-conformity as well as continuous evaluation to ensure effectiveness and efficiency of drug residue monitoring.

## INTRODUCTION

Ivermectins are semi-synthetic macrocyclic lactones derived from avermectin, a chemical naturally produced by *Streptomyces avermitilis* during fermentation. Ivermectins are commonly used for the treatment of diseases caused by endo- and ecto-parasites in various species, including cattle (12, 15, 16, 18).

The main residue in edible tissues of cattle is the un-metabolized drug. After administration, the highest concentrations of residue have been found in liver, followed by fat, kidney and then muscle (18). However, following subcutaneous administration, highest residue concentrations have been reported at the injection site (12). The drug depletion half-life in liver is up to 8 days in cattle, but varies depending on factors such as formulation and route of administration (18, 32).

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) established an ivermectin Acceptable Daily Intake (ADI) of 0–1 µg/kg and a Maximum Residue Level (MRL) of 100 µg/kg for liver and 40 µg/kg for fat as ivermectin B1a, the marker residue (15, 16). A withdrawal time of 28 days is considered acceptable in that it ensures that the 95% upper confidence interval for

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the 99th percentile of cattle treated with 0.3 mg per kg of body weight will have tissue residues below these MRLs (15).

Veterinary drug residue monitoring, which is statistically based, unbiased, and scheduled, involves random sampling, analysis, and reporting of results. It is used to provide information, usually annually, about the occurrence and concentrations of chemical residues in specific populations of food animals or food items. Monitoring data may be helpful for estimating chemical residue trends and identifying high risk circumstances for chemical non-conformities (i.e., chemical residues above an established tolerance or MRL), and to protect consumer health and international trade (6, 7, 17, 29, 30). Residue monitoring programs should ensure, with 95% confidence, that a residue problem over a maximum acceptable prevalence (commonly 1%) will be detected (6, 29).

In Mexico, the Toxic Residues Program is based on several standards and recommendations, such as those published by *Codex Alimentarius*, the Food and Agriculture Organization, World Health Organization, World Organization for Animal Health, Compound Evaluation System of the United States Department of Agriculture (USDA) and the European Directive 96/23/CE (22, 23, 24). As part of the Toxic Residues Program, liver samples from cattle in Mexico were collected between 2006 and 2008 (262, 289 and 110 animals in 2006, 2007 and 2008, respectively) and analyzed for ivermectin residues. None of the samples contained residues above the established MRL (20, 22, 23, 24).

The objective of this study was to determine the prevalence of non-conforming ivermectin residues in cattle slaughtered in federally inspected abattoirs in Nuevo Leon, a northern Mexican state with a reputation for high quality beef and the potential for expanded production (10, 25, 27).

## MATERIALS AND METHODS

The source population was cattle slaughtered in all six federally inspected abattoirs located within Nuevo Leon between mid-November and mid-December, 2009. Cattle of all ages, breeds and origins (including other Mexican states) were included in the study.

A total of 230 liver samples was taken. Because of economic constraints, a 90% level of confidence was selected and

a binomial statistical model was used for the calculation of the desired sample size (1–3, 9, 11). The following formula was used:

$$n = \log \alpha / [\log (1-p)]$$

where  $p = 0.10$  and  $\alpha = 10\%$ .

The number of samples collected from each abattoir was in proportion to its annual slaughter capacity (8). Samples were collected using a circular systematic random sampling plan, based on the number of slaughtering hours per day and week for each abattoir (14). Each abattoir was provided with a sampling schedule that specified the date and time for sample collection. At the designated times, veterinary inspectors assigned to the abattoir by the Agriculture Department of Mexico (SAGARPA) identified an animal on the line for sampling and collected liver samples (at least 250 g; location not specified) that were placed in sterile plastic bags, individually labelled and frozen. Within one week of collection, the frozen samples were shipped to a central laboratory in a cooler with ice packs or dry ice, accompanied by information regarding the sex, age, and origin of the sampled animals.

Samples were analyzed at the “Laboratorio Central Regional de Monterrey” located in Guadalupe, Nuevo Leon, which is accredited by the Mexican Accreditation Entity, based on the quality standard ISO/IEC 17025:2005. Analysis for ivermectin residues was performed by High Performance Liquid Chromatography (HPLC) as specified in the Mexican standard NOM-020-ZOO-1995 (21). Samples that produced positive results were re-tested for confirmation, by use of the same method.

All data were recorded in an electronic database (Microsoft Excel 2007). The prevalence estimates and the binomial exact confidence intervals were calculated by a simple binomial method in Stata 10 MP (Stata Corporation, College Station, TX) and R 2.9.2 software (Statistics Department of the University of Auckland, New Zealand). Descriptive statistics and graphics were calculated and developed using Epi Info™ v.3.5.1 (Centers for Disease Control and Prevention, Atlanta Georgia).

## RESULTS

In total, 234 cattle liver samples were randomly collected during the study period of mid-November to mid-

December, 2009. Most of the cattle originated from Nuevo Leon ( $n = 178$ ; 76%), but others were from Tabasco, Coahuila, Zacatecas, Michoacan, Aguascalientes, Durango, San Luis Potosi, Tamaulipas and Yucatan. The mean age of the animals was 26.8 months with a standard deviation of 9.5 months. Fifty-four percent of the animals were female and 46% were castrated males.

Most samples ( $n = 227$ ; 97%) contained no detectable levels of ivermectin residue. There were four different levels (concentrations) among the samples that contained at least some residue (Table 1). Only one sample contained a non-conforming level (149  $\mu\text{g}/\text{kg}$ ). Samples containing at least some ivermectin residue (i.e., both conforming and non-conforming) originated from seven batches of cattle slaughtered within three of the six abattoirs. The average size of these batches was 30 animals (range 4–90); they originated from Nuevo Leon (3), Tabasco (2) and Tamaulipas (1); the origin of one of the positive samples was unknown. Four of the seven animals with non-zero concentrations were male; the average age of affected animals was 43 months (range 23–80 months). The non-conforming sample came from a 72 month-old male from Nuevo Leon that was from a batch of 4 animals.

## DISCUSSION

The observed prevalence of non-conforming ( $>100 \mu\text{g}/\text{kg}$ ) ivermectin residues in cattle liver in this study was small (0.43%) and the vast majority of samples (97%) contained no detectable residue. The 95% confidence intervals of the prevalence of non-conforming residue obtained during this study was consistent with the confidence intervals for ivermectin residue from data gathered during the 2006–2008 residue monitoring program in Mexico (95% exact binomial confidence interval: 0, 0.006). We focused on this region of Mexico (Nuevo Leon) and tested animals at this time of year (mid-November to mid-December) because of suspicions that the frequency of ivermectin use was high. However, we did not attempt to measure the extent of ivermectin use in the study population. The consistency of our findings with those from the general slaughter population of Mexico (23–25) suggests that if the frequency of use was indeed high in this region, appropriate drug withdrawal

**TABLE 1. Prevalence and 95% exact binomial confidence intervals for observed ivermectin residue levels in bovine liver samples**

Ivermectin residue level ( $\mu\text{g}/\text{kg}$ )	Number of samples	Prevalence	Standard error	Binomial exact confidence interval (95%)
No detectable residues	227	0.97	0.011	0.940–0.988
>0– <5	4	0.017	0.008	0.005–0.043
7	1	0.004	0.004	0.000–0.024
20	1	0.004	0.004	0.000–0.024
149 <sup>1</sup>	1	0.004	0.004	0.000–0.024

<sup>1</sup>Exceeds the MRL of 100  $\mu\text{g}/\text{kg}$

times and other residue avoidance practices appear to have been observed, for the most part.

All three North American countries monitor veterinary drug residues in cattle. In Canada, the MRL for ivermectin is 70  $\mu\text{g}/\text{kg}$  in liver, lower than the limit established by JECFA (13) and used by Mexico. Between 2006 and 2009, the Canadian National Chemical Residue Monitoring Program (NCRMP) did not report any non-conforming ivermectin residues in either Canadian or imported cattle samples (4, 5). Between 2005 and 2007 in the United States, sampling identified non-conforming ivermectin residues in samples from various cattle production classes (in 2005: 1/302 for bulls, 1/337 for heavy calves, 1/303 for steers, and 2/298 for non-formula fed veal; in 2006: 1/173 for non-formula fed veal and in 2007: 1/316 for bulls, 3/200 for heavy calves, and 1/1046 for steers). In 2008, no non-conforming ivermectin residues in cattle were detected through sampling in the United States (29–31), although one non-conforming sample from Uruguay was detected by sampling of imported products (32).

In May 2010, a recall class II (low risk) involving ivermectin residues in beef products was reported by the USDA. The recall involved cooked beef products originating from a federally inspected plant in Brazil; this plant was delisted and its beef products prohibited from entering the United States (30, 33).

Economic losses resulting from products that must be destroyed when non-conformities are detected (7) as well as the loss of consumer confidence are im-

portant consequences at a national level. Furthermore, non-conformances could result in the establishment of international trade barriers (6). Exporting countries have the responsibility to protect both public health and markets by complying with international requirements. Like other meat exporting countries, Mexico must be aware of this situation (28, 34) and focus on minimizing the occurrence of non-conforming residues of all regulated chemicals, including ivermectin, while using all its available resources efficiently.

We do not know the underlying reason(s) for the non-conformity in the single animal detected in this study. The number of non-conformities and even of positive results was insufficient to allow the calculation of risk factors associated with ivermectin residues in this study. The likelihood of use of ivermectin in cattle depends upon the farmer's and / or veterinarian's perception of the likelihood of parasite infestation of the cattle, which tends to be seasonal (19). Since the use of ivermectin is expected to be different at different times of the year, the results from this study are not likely to be representative of populations slaughtered throughout the year. However, late autumn (November / December) is likely to be a season of greater use of ivermectin in cattle, as this season is considered to be a time of high occurrence of some external parasites in cattle. This suspected seasonality could be related to the non-conformance reported (7).

Use of veterinary drugs in accordance with the manufacturers' recommendations, in conjunction with good veterinary practices, should prevent occurrence of tissue residues that exceed

the established MRLs (7, 34). In this study, non-conformance with respect to ivermectin residues was rare in slaughter cattle in Nuevo Leon. These results are consistent with one of the main objectives of residue monitoring programs in general, which is to verify that non-conforming residues are infrequent and consequently that the health of consumers is protected (7). However, it should be recognized that the Mexican toxic residues program and the present study include samples exclusively from federally inspected plants, which represent approximately 8% of the total number of abattoirs and a small proportion of the total annual production in Mexico (26).

We strongly recommend continual assessment of the monitoring program to validate its efficacy, and efficiency as well as the inclusion of priority chemicals and further recommend future studies to identify risk factors associated with ivermectin residue.

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