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Spatial-temporal Distribution of the *2007 Melamine-associated Nephrotoxic Renal Failure Outbreak* among Pets and Factors Associated with Pet Survival

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SUMMARY

This study describes the spatial-temporal distribution of the 2007 melamine-associated nephrotoxic renal failure outbreak among pets and factors associated with pet survival. A retrospective case series was performed using melamine-associated consumer complaint data obtained from United States (U.S.) Food and Drug Administration. Data represented 10,109 pets (5,284 dogs and 4,408 cats). Spatial-temporal distributions and factors associated with pet characteristics and survival were analyzed using EpiInfo version 3.2 and SAS version 9.2. Overall, 194 pet food brands were allegedly contaminated with melamine, with seven major brands affecting 71% of the pets. The reports were received between March and July, 2007 and came from all 50 states. The same percentage of pet deaths (45%) was observed in cats and dogs. Kidney failure was the commonest (27%) clinical sign reported. Pet survival was significantly ($P < 0.05$) associated with region, reported renal failure, hospitalization, and interaction between region and period of case reporting. Pets hospitalized and those without reported renal failure were 1.2 and 1.3 times more likely to survive than those not hospitalized (OR, 1.22; 95% CI, 1.08, 1.39, $P < 0.0020$) and those with renal failure (OR, 1.27; 95% CI, 1.09, 1.47, $P < 0.0016$), respectively. Overall, pets from the Northeast and the South were more likely to survive than those from the Midwest or West, particularly during the first period of case reporting. Survival was not influenced by pet species or pet food brands. Using the FDA consumer complaints surveillance data, this study describes the spatial-temporal distribution of reported melamine-associated nephrotoxicity among cats and dogs during 2007 in the U.S. and identifies variables associated with survival of affected pets.

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INTRODUCTION

A large outbreak of pet food-associated nephrotoxic renal failure occurred in early 2007, affecting dogs and cats in the United States (U.S.) *(1, 7, 25, 26).* Melamine in wheat gluten, rice protein, and corn gluten used as pet food ingredients, imported from China, was implicated in the outbreak *(13).* Melamine is a chemical used primarily for melamine resins, although it is marketed as a fertilizer for its high nitrogen content *(6, 20).* Melamine resin is widely used for surface coatings and decorative laminates such as countertop material *(3).* Also, melamine/ formaldehyde resin can be used as a film former in cosmetic formulations, although no current such uses are reported *(2).*

Respiratory distress, bleeding in the lungs, significant weight loss, and macrophage influx into the alveoli were observed during melamine inhalation studies in rats *(2).* A 2-year chronic feeding study in rats at concentrations ≤ 10% produced little toxicity *(18).* Similar results were found in dogs at concentrations of 2.5, 3, and 5%. Reproductive toxicity was evaluated in rats through two generations with no evidence of reproductive effects *(2).* Case reports in the clinical literature have reported sensitization to melamine/formaldehyde resin, not all of which were attributed to the presence of formaldehyde. When available data on melamine were reviewed, no irritation or sensitization was produced by 1% (aqueous) melamine in guinea pigs. In an oral carcinogenesis assay in male rats, melamine caused transitional-cell carcinomas of the urinary bladder but produced no tumors in female rats *(2).* Melamine and cyanuric acid were allegedly added by suppliers in China to falsify the protein content of the pet food ingredients *(21, 24).* Neither melamine nor cyanuric acid is particularly toxic alone; however, in combination, insoluble crystals of melamine-cyanurate form, and these crystals obstruct and damage renal tubules, causing nephrotoxic renal failure *(11, 34, 35, 37).*

The 2007 nephrotoxicity outbreak and the ensuing pet food recalls provoked extensive media coverage and reports of animal deaths, causing nationwide uncertainty and concern for pet owners *(5, 6, 7, 22).* Although the incident was a pet food incident, it also tested the same systems the U.S. has in place for handling such problems in human food *(10, 33).* For instance, fish, hog and poultry feeds have been found to be contaminated with melamine *(27).* During the incident, the U.S. Food and Drug Administration (FDA) created countrywide complaints surveillance for pet food recalls and cases of nephrotoxicity associated with melamine *(5, 13, 14).* Approximately 10,000 consumer complaints were received by the FDA countrywide *(13).* To date, no official outbreak findings have described the spatial-temporal distribution, pet types affected, pet food brands consumed, clinical signs, or pet hospitalization status, during the 2007 melamine-associated nephrotoxicity outbreak in the U.S. Also lacking is information on factors that influenced pet survival during the outbreak. Therefore, on the basis of the FDA consumer complaints surveillance data, this study describes the spatial-temporal distribution of reported melamine-associated outbreak of nephrotoxicity among pets (cats and dogs) during 2007 in the U.S. and identified variables associated with survival of affected cases.

MATERIALS AND METHODS

Data source

FDA consumer complaint data were used *(14).* Consumer complaints are FDA's primary surveillance tool for highlighting existing problems and long term trends of a disease outbreak. During the 2007 melamine-associated outbreak, pet owners were urged to report complaints through the Consumer Complaint Reporting System (CCRS), by either calling FDA (8 a.m. to 4:30 p.m. Monday through Friday) or via mailed-in complaint-reporting forms. The information obtained by FDA included affected pets and consumed pet food brand names, lot numbers, and their associated Universal Product Codes (UPC). Additional information provided by consumers included pet treatment by veterinarian and their reports, date illness was first noticed, and clinical signs. The information provided by consumers was compiled by FDA's Consumer Complaint Coordinators (CCCs) throughout the U.S. and Puerto Rico *(14).*

For this study, data were obtained from FDA in accordance with the Freedom of Information Act (FOIA) *(15).* We made a FOIA request to FDA (Division of the Freedom of Information Offices, +1 301.796.3900; Food and Drug Administration, Division of Freedom of Information, Office of Shared Services, Office of Public Information and Library Services, 12420 Parklawn Drive, ELEM-1029). We also included the Requestor's name, address, and telephone number and a description of the records being sought. The data obtained included pet food brand and product descriptions; pet type (dog/cat); adverse event (whether pet died, had life-threatening-condition/injury or did not have life-threatening-condition/injury); when adverse event occurred; veterinary visit/care, pet hospitalization; and pet-owner diagnosed health status and clinical signs of nephrotoxicity (such as renal failure, vomiting, diarrhea and lethargy). The date of the consumer complaints to FDA and state code indicating location of complaint were also collected.

Modifications and assumptions made on the FDA data

Under the consumer complaint description of, "adverse event," pets that had a life-threatening condition/injury and pets that did not have life-threatening condition/injury were both categorized in this study as "pets that survived," and pets that died were categorized as "pets that did not survive." Further, the number of pets affected was determined from the owners' reports on pet type. It is assumed that all pets reported by owners were suspect cases.

Descriptive analysis

Using EPI INFO version 3.2a and SAS version 9.2b software, the distributions of pet species, implicated pet food brands, veterinary visit, pet hospitalization, period of reporting cases to FDA, and the pet owner-diagnosed clinical signs (renal failure, vomiting, diarrhea, and lethargy) were described, using numerical summaries.

Spatial and temporal analysis of the epidemic

EPI INFO version 3.2a was used to display the temporal distribution of this outbreak, which provided a description of the magnitude of

TABLE 1. Descriptive statistics of consumer reported variables for the 2007 melamine-associated outbreak of nephrotoxicity among pets in the United States (N = 10,109)

VARIABLE		% (number)	% (number) of pets that survived 45 (4,248)	% (number) of pets that did not survive 55 (5,193)
PETS				
	DOG	52.3 (5,152)	45 (2,311)	55.1 (2,841)
	CAT	43.6 (4,289)	45 (1,937)	54.8 (2,352)
	OTHERS	0.03 (3)	-	-
	UNKNOWNS	4.9 (414)	-	-
RENAL FAILURE				
	YES	26.7 (2,703)	41 (1,083)	58.87 (1,550)
	NO	11.1 (1,126)	40 (450)	59.61 (664)
	UNKNOWNS	14.1 (1,429)	-	-
VISIT TO VETERINARIAN				
	YES	74.7 (7,554)	46 (3,397)	54.49 (4,068)
	NO	11.1 (1,126)	40 (450)	59.61 (664)
	UNKNOWNS	14.1 (1,429)	-	-
HOSPITALIZATION				
	YES	25.3 (2,560)	50 (1,268)	49.98 (1,267)
	NO	31.2 (3,149)	45 (1,392)	55.43 (1,731)
	UNKNOWNS	43.5 (4,399)	-	-
REGION				
	MIDWEST	25 (2,515)	41 (1,008)	59.27 (1,467)
	WEST	22 (2,203)	43 (910)	57.03 (1,208)
	NORTHEAST	19 (1,888)	50 (934)	49.68 (922)
	SOUTH	30 (3,073)	47 (1,393)	53.24 (1,586)
	PUERTO RICO	0.1 (13)	23 (3)	76 (10)
	UNKNOWNS	4 (417)	-	-
PET FOOD BRANDS				
	A	20 (1,995)	46 (896)	53.93 (1,049)
	B	14 (1,405)	43 (581)	56.80 (764)
	C	12 (1,218)	45 (539)	54.78 (653)
	D	11 (1,090)	44 (468)	55.89 (593)
	E	6 (614)	48 (287)	52.01 (311)
	F	5 (509)	46 (230)	54.09 (271)
	G	3 (328)	47 (150)	53.27 (171)
	OTHERS	23 (2,339)	45 (1,063)	55 (1,276)
	UNKNOWNS	6 (611)	-	-
PERIOD OF CASE REPORTING				
	PERIOD 1	62 (6,115)	46 (2,813)	54 (3,302)
	PERIOD 2	34 (2,744)	43 (1,180)	57 (1,564)
	PERIOD 3	4 (582)	44 (255)	56 (327)

reports of nephrotoxicity. For the temporal distribution, an epidemic curve was generated using the date cases were reported (x-axis) and the number of cases (y-axis) as the epidemiological unit of interest. The date the first case was reported to FDA was recorded as the start date for the outbreak. The number of cases reported each day was plotted against a time axis (date of the month). Also, a spatial map was used to describe the outbreak spread by state and region, using the number of cases reported from each state per 10,000 pets (incidence) *(40).* Data for the denominator (number of pets per state) was from the national pet owners' survey *(40).* The regions, mapped according to U.S. census regions and divisions, were West, Midwest, Northeast, and South (http://www.eia.doe.gov/emeu/reps/maps/us_census.html). Cases reported from Puerto Rico were left out of the analysis because of the relatively small numbers reported. For mapping, the Uniform classification scheme was used to determine break points, with an incidence class width of 156.

Chi-square analysis

To assess associations among variables in the data set, a^2 test of independence was used. Collinearity among the independent variables was evaluated. Additionally, a comparison of equality of proportions of pets that survived among independent variables examined was performed using a^2 test. The variables were (1) pet species (dog or cat); (2) regions from which cases were reported (West, Midwest, Northeast or South); (3) renal failure (no or yes); (4) visits to veterinarian (no or yes); (5) pet hospitalization (no or yes) and (6) pet food brands (A, B, C, D, E, F, G). Ten other different pet food brands comprising 23% (2,339) of pet foods were classified as "other," while 6% (611) were categorized as unknown.

Logistic regression analysis

This analysis was performed to identify pet characteristics that were significantly associated with pet survival (survival or no survival). Covariates were type of pet (dog or cat); region (Western, Midwestern, Northeast or South); renal failure (no or yes); visit to veterinarian (no or yes); pet hospitalization (no or yes); and pet food brands (A, B, C, D, E, F, G). Pet brands classified as "other" or "unknown" categories were dropped from further analysis because of the relatively small numbers compared to the other 7 major pet food brands. Collinearity among the independent variables was taken into account during model building and determined the criteria by which the main effects were dropped from the model, in addition to the AIC and *P*-values. For all final comparisons, a value of $P < 0.05$ was considered significant. The stepwise logistic regression model building approach as described by Hosmer and Lemeshow *(19)* was followed. The reference levels chosen in the main effects/independent variables included region (reference group: Midwest), renal failure (reference group: Yes) and hospitalization (reference group: No). Using a reduced model based upon backwards elimination, the full main effects model was assessed first, followed by interactions. The four main effects and interaction that formed our final multiple logistic regression model were renal failure, hospitalization, region, period of case reporting and interaction between region and period of case reporting. Also assessed was the goodness-of-fit of the model based on AIC and the likelihood ratio test. A parameter estimate with a value of $P < 0.05$ was considered significant for the model.

RESULTS

Descriptive analysis

Table 1 summarizes descriptive statistics of all variables included in the study: % of pet species, % with renal failure, % of pets that visited a veterinarian, % of pets that were hospitalized, distribution by region and pet food brand and % survival. Other pet food brands (23%, 2,339) reported included ten different brands which ranged in % from 0.4% to 2%; two brands (comprising 6% of pet food brands) were categorized as unknown.

Kidney failure (27%, 2,703) was the most pet-owner diagnosed clinical sign of nephrotoxicity, and 41% (1,083) of pets reported with kidney failure survived. Other clinical signs were diarrhea (0.6%), vomiting (0.4%), lethargy (0.2%), lethargy and vomiting (0.3%), and 'combination of symptoms' (vomiting and diarrhea, and loss of weight and loss of appetite) (1.1%). However, 4% (409) of the cases had unknown/unreported clinical signs. Further, several pet brands were reported to have been contaminated in the 2007 nephrotoxicity outbreak. Overall, 194 pet brands were contaminated; however, seven major brands affected 71% of the pets, and 23% of pet food brands were categorized as "other" and 6% as "unknown" (Table 1).

Temporal and spatial analysis

The first case reported to FDA during the 2007 melamine associated pet food recall was on March 1, 2007, while the last case was reported on July 12, 2007 (Fig. 1). The number of reported cases rose sharply, with most cases reported in March, and declined over time. Cases peaked (66%, 4,889) on March 22, 2007. The epidemic curve was characterized by three distinct periods (named period 1, 2 and 3) in which cases reported to FDA had a similar distribution pattern (Fig. 1). The distribution of cases followed a distinct pattern in which the fewest cases were reported on Saturdays and Sundays.

The spatial distribution of the affected pets per 10,000 pets by state and region indicates that although the outbreak was widespread in all 50 states, the highest incidence (≥ 516 cases per 10,000 pets) were from Oregon (OR), Kentucky (KY), Missouri (MO), Maine (ME), and New Hampshire (NH) (Fig. 2). Meanwhile, the lowest numbers of reports (≤ 46 cases) were from the states of South Dakota (SD), Wyoming (WY), Utah (UT), New Mexico (NM), Pennsylvania (PA), Washington, D.C., and Virginia (VA) (Fig. 2). Among the United States' four Census Regions and Divisions—West, Midwest, Northeast, and South— the incidences reported were as follows: South (30%, 3,073), Midwest (25%, 2,515) West (22%, 2,203), and Northeast (19%, 1,888) (Fig. 2). Also, a few cases (0.1%, 13) were reported from Puerto Rico.

Chi-square analysis results

A chi-square test for equality of proportions among pets that survived the 2007 melamine associated nephrotoxicity outbreak was performed; results are summarized in Table 2. There was a statistically significant difference ($P < 0.05$) between proportions of pets that survived among pets that had or did not have the following characteristics: renal failure, visit to veterinarian, hospitalization,

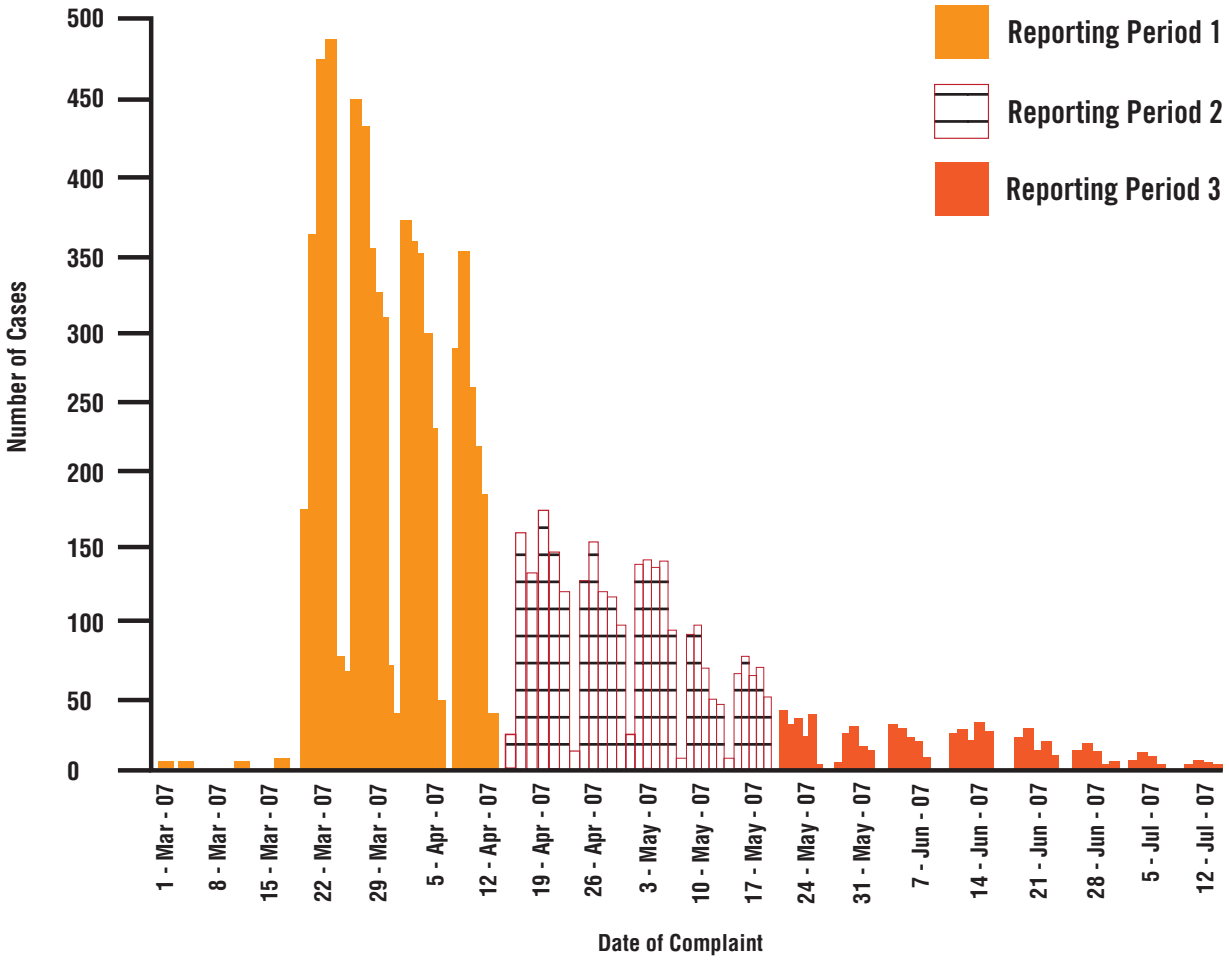

Figure 1. Temporal distribution of 10,109 pets affected during the 2007 melamine-associated nephrotoxicity outbreak

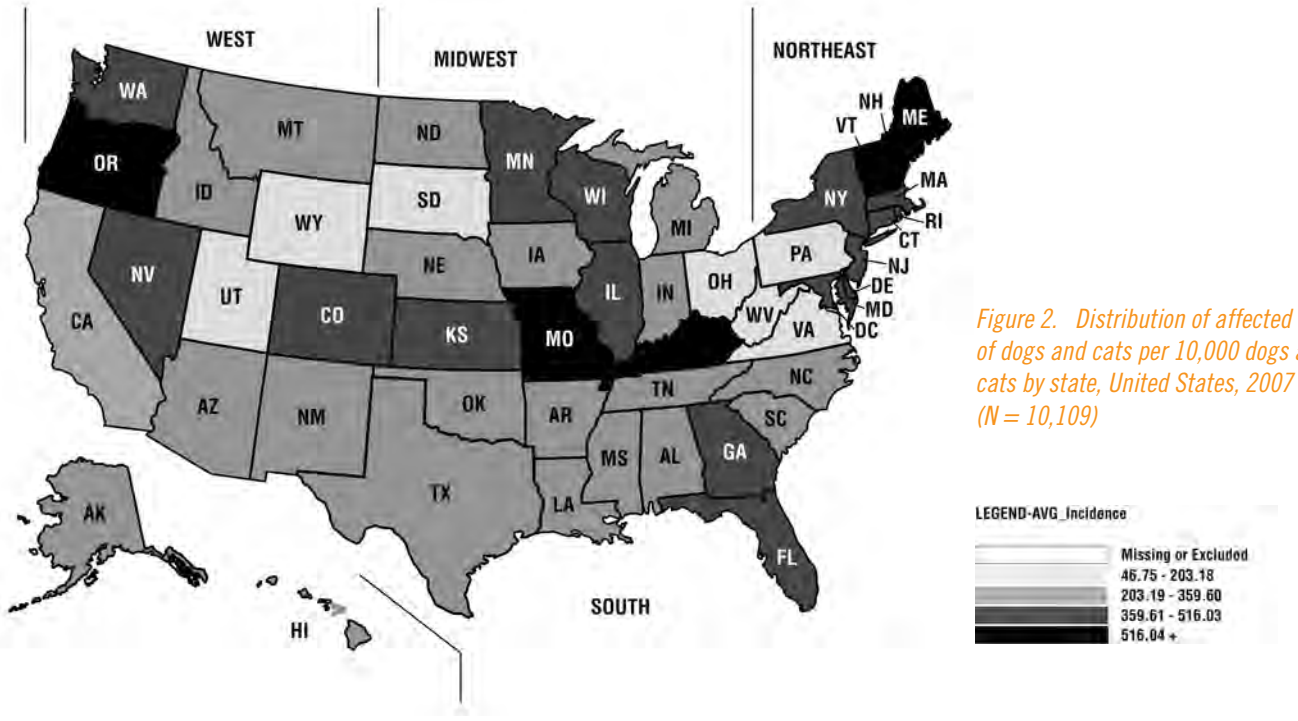

Figure 2. Distribution of affected cases of dogs and cats per 10,000 dogs and cats by state, United States, 2007 (N = 10,109)

TABLE 2. Chi-square test for equality of proportions among pets that survived during the 2007 melamine-associated nephrotoxicity outbreak in the United States

VARIABLE		% (number) of pets that survived	Total number of pets	Chi-square (X^2)	*P*-value
PETS		45 (4,248)	9,441	0.00	0.994880
	DOG	45 (2,311)	5,152		
	CAT	45 (1,937)	4,289		
RENAL FAILURE			9,441	19.11	< 0.0001*
	YES	41 (1,083)	2,633		
	NO	46 (3,165)	6,808		
VISIT TO VETERINARIAN			8,579	13.93	< 0.0001*
	YES	46 (3,397)	7,465		
	NO	40 (450)	1,114		
HOSPITALIZATION			5,685	14.02	< 0.0001*
	YES	50 (1,268)	2,563		
	NO	45 (1,392)	3,122		
REGION			9,428	42.77	< 0.0001*
	MIDWEST	41 (1,008)	2,475		
	WEST	43 (910)	2,118		
	NORTHEAST	50 (934)	1,856		
	SOUTH	47 (1,393)	2,979		
PET FOOD BRANDS			6,963	6.26	0.3948
	A	46 (896)	1,945		
	B	43 (581)	1,345		
	C	45 (539)	1,192		
	D	44 (468)	1,061		
	E	48 (287)	598		
	F	46 (230)	501		
	G	47 (150)	321		
PERIOD OF CASE REPORTING			9,441	7.14	0.0281*
	PERIOD 1	46 (2,813)	6,115		
	PERIOD 2	43 (1,180)	2,744		
	PERIOD 3	44 (255)	582		

and difference based on location (region) and period of case reporting. However, no significant difference ($P > 0.05$) in percent survival was reported with regard to pet type and pet food brand. Of the pets that survived, those without renal failure (46%, 3,165) and those that visited a veterinarian (46%, 3,397) had higher percent survival than pets with renal failure (41%, 2,633) and pets that did not visit a veterinarian (40%, 450), respectively. Also, of the pets that survived, hospitalized pets had a higher percent pet survival (50%, 1,268) than those that were not hospitalized (46%, 1,392). Among the regions, the Northeast had a higher percent pet survival (50%, 934) than the South (47%, 1,393), West (43%, 910), and Midwest (41%, 1,008). Between the three periods of time when cases were reported to FDA, cases reported during period 1 (during the period of March 1 to April 12) had the highest percent survival (46%, 2,813) compared to those reported during period 2 (April 19 to May 17), which had a survival of 43% (1,180) and those reported in period 3 (May 24 to July 12), which reported a survival of 44% (255) (Table 2).

Logistic regression results

Results of the chi-square test of independence to assess collinearity between independent variables showed that a number of the variables had significant associations; this could explain why only four variables ended up in the final multiple logistic regression model. For instance, pet species was significantly associated ($P < 0.05$) with period of reporting, renal failure, and the pet food brands. Also, period of reporting was significantly associated ($P < 0.05$) with region, renal failure, and pet food brands. Region was significantly associated ($P < 0.05$) with renal failure, pet brands, visit to veterinarian, and hospitalization. Renal failure was also significantly associated ($P < 0.05$) with pet food brands, and pet food brand was significantly associated ($P < 0.05$) with visit to veterinarian and hospitalization. Visit to a veterinarian was significantly associated ($P < 0.05$) with hospitalization.

Table 3 shows the univariate logistic regression analysis to assess association between pet survival and the independent variables. Pet survival was significantly associated ($P < 0.05$) with renal failure, hospitalization, region, and period of case reporting. More specifically, pets that were hospitalized were 1.3 times more likely to survive than pets that were not hospitalized (OR, 1.25; 95% CI, 1.12, 1.38, $P < 0.0001$). Pets without renal failure were 1.2 times more likely to survive than pets with renal failure (OR, 1.24; 95% CI, 1.14, 1.36, $P < 0.0001$). In comparison to the Midwest (selected as the reference region because it reported the fewest pets that survived), pets reported from the West were 1.1 times less likely to survive (OR, 1.10; 95% CI, 0.98, 1.23, $P < 0.125$). Also, pets from the Midwest were 1.5 times less likely to survive, compared to pets from the Northeast (OR, 1.47; 95% CI, 1.31; 1.67, $P < 0.0001$), while pets from the Midwest were 1.3 times less likely to survive than pets from the South (OR, 1.29; 95% CI, 1.15, 1.42, $P < 0.0001$. Additionally, pets reported during period 1 were 1.2 times more likely to survive than pets reported during period 2 (OR, 1.2; 95% CI, 1.03, 1.36, $P < 0.0211$), and pets reported during period 1 were 1.2 times more likely to survive than pets reported during period 3, although this difference was not statistically significant (OR, 1.24; 95% CI, 0.95, 1.62, $P = 0.1210$).

Table 4 shows the final multiple logistic regression model assessing the association between pet survival and independent variables that met the 5% threshold. The P-values reported in Table 4 were obtained from Type III analysis of effects. The independent variables renal failure, hospitalization, and the interaction between region and period of case reporting were statistically significantly ($P < 0.05$) associated with pet survival. During period 1 of case reporting (March to April), % survival of pets in the four regions was statistically significantly different overall ($P < 0.001$; = 60.7) and was as follows: Northeast (58.5%), South (54.3%), West (43.7%) and Midwest (40.1%). During period 2 of case reporting (April to May), the % pet survival between the four regions followed a similar trend (Northeast 46.4%; South 45.7%; West 46.9%; and Midwestern 39.7%), except the difference was not statistically significant ($P = 0.3365$; 3.38). During period 3 of case reporting (May to July), again the % pet survival between the four regions followed a similar trend (South 50.5%, Northeast 48.3%; West 40% and Midwest 23.5%), except the difference was statistically significant ($P = 0.0409$; = 8.26), and the South had the highest % survival. Complete case analysis was used to obtain the final multiple logistic regression model, resulting in a final sample size of 4,048 and the Hosmer and Lemeshow (19) goodness-of-fit test suggested that the model was adequate ($P = 0.8698$).

DISCUSSION

It is unclear when the 2007 melamine-associated nephrotoxicity outbreak in dogs and cats began. However, the epidemic curve showed that the first case reported to the FDA was on March 1, 2007 and that the reports to FDA occurred over four months, with the last case reported on July 12, 2007. The epidemic curve was characterized by distinct periods in which cases were reported to the FDA in clusters. The first month of reporting (March) had the largest number of cases reported probably due to anxiety *(12, 36, 39)*, with cases peaking on March 22, 2007. The low numbers of cases reported in later months were probably due to the lower media coverage during this later period *(4)* as well as the FDA preventive-control outbreak and recall response strategies *(9)*. For example, from April to July the FDA actively implemented and monitored recalls; provided up-to-date information on the outbreak and recalls to consumers; and prevented additional contamination by instituting import alerts to prevent further import of contaminated ingredients. The FDA also coordinated rapid identification of the causative agent to minimize pet food contamination and thus nephrotoxicity *(13)*.

The spatial distribution of reports indicated that the outbreak was widespread in all 50 U.S. states, which is a characteristic pattern of outbreak explained by the fact that the melamine was ingredient-based and therefore widely distributed in all states *(2, 4, 16)*. In ingredient-based outbreaks, a contamination affects many different products that are distributed through various channels and consumed in different settings *(2, 16)*. The melamine-contaminated pet food ingredients, including wheat gluten, rice protein, and corn gluten, were used in the production of many pet foods and distributed to retail establishments nationwide. Such extensive distribution of pet food ingredients probably influenced the nationwide distribution of the outbreak. Also, the widespread distribution of the cases reported could indicate that all

TABLE 3. Results of univariate regression analysis of association between pet survival and independent variables during the 2007 melamine-associated nephrotoxicity outbreak in the United States

VARIABLES	CATEGORY	DEGREES OF FREEDOM	NUMBER OF PETS	ODDS RATIO (95% CONFIDENCE LIMIT)	*P*-VALUE
PETS	DOG VS. CAT	1	9,441	0.99 (0.910–1.072)	0.7663
RENAL FAILURE	NO VS. YES	1	9,441	1.24 (1.135–1.362)	<.0001*
VISIT TO VETERINARIAN	YES VS. NO	1	8,579	1.23 (1.084–1.400)	0.0014*
HOSPITALIZATION	YES VS. NO	1	5,658	1.25 (1.120–1.382)	<.0001*
REGION		3	9,428		<.0001*
	WEST VS. MIDWEST			1.10 (0.975–1.233)	0.1253
	NORTHEAST VS. MIDWEST			1.47 (1.306–1.664)	<.0001*
	SOUTH VS. MIDWEST			1.29 (1.148–1.424)	<.0001*
PET FOOD BRANDS		6	6,963		0.4750
	E VS. D			1.17 (0.956–1.430)	0.1273
	A VS. D			1.08 (0.931–1.258)	0.3030
	C VS. D			1.05 (0.886–1.235)	0.5972
	B VS. D			0.96 (0.819–1.133)	0.6541
	G VS. D			1.11 (0.865–1.428)	0.4083
	F VS. D			1.08 (0.869–1.331)	0.5045
PERIOD		2	9,441		
	1 VS. 2			1.18 (1.025–1.355)	0.0211*
	1 VS. 3			1.24 (0.945–1.620)	0.1210

*P values associated with effects and P-values showing associations at $P < 0.05$ on screening at $P \leq 0.25$; n = number of observations used; df = degrees of freedom; Period = Period of Case Reporting.

TABLE 4. Results of final logistic regression model between pet survival and independent variables, during the 2007 melamine-associated nephrotoxicity outbreak in the United States; Type III Analysis of effects (N = 4048)

VARIABLES	DEGREES OF FREEDOM	Chi-square (X^2)	*P*-VALUE
RENAL FAILURE	1	10.01	0.0016
HOSPITALIZATION	1	9.80	0.0017
REGION 3	3	7.69	0.0528
PERIOD	2	3.76	0.1526
REGION PERIOD*		14.83	0.0216

*Final model was based on complete case analysis with sample size of N = 4048.

states consumed similar pet food brands produced or packaged by a few pet food manufacturers nationwide. For instance, FDA reports indicated that only seven major pet food brands were associated with the majority (71%) of the cases reported *(13).*

It is unclear why states such as Oregon, Kentucky, Missouri, and Maine reported the highest incidence (> 516 per 10,000 pets). It is possible that this was because these states are among those with the highest percentage of pets in the U.S. *(40).* Alternatively, the pets in these states could have been at greatest risk of nephrotoxicity or the pet owners in these states may have been more concerned and vigilant in reporting to FDA. There is a possibility that the number of cases reported from these states could have been biased by the FDA consumer complaint campaigns and increased consumer awareness and anxiety due to extensive media reporting *(17).* Also, the relatively high number of cases reported from these states could have been confounded by other variables on which we did not collect information, such as types of veterinary practice and previously reported nephrotoxicity by the veterinary practice in these states, as these characteristics vary by pet-owning households *(38, 41).*

The large number of pets affected and percent of deaths reported in this study is in agreement with related findings regarding the 2007 melamine-associated pet food recall reported by the American Association of Veterinary Laboratory Diagnosticians (AAVLD). A survey by AAVLD *(34)* reported 347 pet cases from April 5 to June 6. These cases included 235 cats and 112 dogs, with percent deaths of 61% and 74%, respectively. Interestingly, in this study, as in ours, pet species was not significantly associated with pet survival, yet species differences during the 2007 nephrotoxicity outbreak event has been reported elsewhere *(32, 34),* indicating that cats were likely to be affected more severely than dogs. To date, the significance of species-difference as regards susceptibility to melamine-cyanurate toxicity is unknown. The findings in the current study may have been influenced by the fact that data were reported by pet owners *(23),* whose diagnoses and reports needed professional verification. Most data collected from the FDA could reflect pet owner anxiety, and possible misdiagnosis.

Many major pet food companies in the US are subsidiaries of gigantic multinational corporations that engage in co-packing *(32),* a common arrangement in these corporations, in which one company makes the food but uses another's label *(29).* For example, 100% of pet food brand A was actually produced by two different pet food brands, both of which were associated with the outbreak and were also producing pet food for dozens of private label and brand names *(31).* According to Neela *(28),* the advantage of using a co-packer is that it can buy ingredients in larger bulk than any one pet food maker could on its own, thus making the process cheaper and the profits larger. However, this bulk purchase and the production associated with co-packing could predispose the ingredients to cross contamination *(30).* Co-packing arrangements could explain the presence of melamine in virtually all the affected products as well as why pet survival was similar across pet food brands.

The interaction between region and period of case reporting was statistically significantly associated with pet survival during period 1 (March to April) and period 3 (May to July) but not during period 2. It is interesting that pet survival by region during period 1, when the majority of cases were reported, was similar to that observed overall (Table 1). It is possible that the smaller number of cases reported

during periods 2 and 3 influenced the results of pet survival by region. Of note was the fact that the Midwestern region consistently reported a lower survival overall and during all the 3 periods of case reporting. This could be associated with a difference in veterinary care services available in the different regions or purely due to differences in pet population or lifestyles related to pet ownership by people living in the different regions of the country *(42).*

Interpretation and generalizability of these data are limited by the fact that data used were pet owner reported. In general, the conditions, signs, and symptoms reported could not be verified by a technical person (veterinarian). Further, this study was a retrospective case series, and the data collected had missing information such as awareness of veterinary clinics, types of veterinary practice, and previously reported nephrotoxicity by the veterinary practice. The availability of such information would have provided a better understanding of the outbreak and the risk factors associated with pet survival of melamine-associated nephrotoxicity. Regardless of these limitations, this study provides reflections and lessons learned or that could be avoided in future similar outbreaks. Using the FDA consumer complaints surveillance data, the study describes the spatial-temporal distribution of reported melamine-associated outbreak of nephrotoxicity among pets (cats and dogs) during 2007 in the U.S., provides information on how widespread the outbreak was, and identifies variables associated with survival of affected pets.

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