Selenium Elimination in Pigs after an Outbreak of Selenium Toxicosis

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Selenium elimination in pigs after an outbreak of selenium toxicosis

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Abstract. In May 1996, 150 grower pigs in 5 California counties were exposed to selenium-contaminated feed distributed by a single feed company. Feed samples from 20 herds had a mean selenium concentration of 121.7 ppm dry weight (range, 22.1–531 ppm). In San Luis Obispo County, 52 pigs in 24 herds were exposed to the feed, and 8 pigs died with signs of paralysis. Bilateral symmetrical poliomyelomalacia involving the ventral horns of the cervical and lumbar intumescence was evident on histologic examination of spinal cord from affected pigs. Of 44 surviving exposed pigs, 33 (75%) exhibited signs of selenosis, including anorexia, alopecia, and hoof lesions. Thirty-nine of 44 pigs (88.6%) had elevated (>1 ppm) blood selenium concentrations. Surviving exposed pigs were changed to a standard commercial ration containing approximately 0.5 ppm (dry weight) selenium. Blood selenium concentrations were determined weekly for 46 days following removal of the contaminated feed and were compared with values of 20 control pigs fed a standard commercial ration. Mean (±SD) blood selenium concentrations of exposed pigs were 3.2 ± 2.6 ppm at the initial sampling and 0.4 ± 0.1 ppm after 46 days. Mean blood selenium concentrations of ≤ 0.3 ppm for control pigs at all samplings were significantly lower ($P < 0.001$) than concentrations for exposed pigs. Muscle and liver samples of 22 of the 44 exposed pigs were collected at slaughter approximately 72 days after withdrawal of the selenium-contaminated feed. Muscle samples had a mean selenium concentration of 0.36 ppm (wet weight). Liver samples had a mean selenium concentration of 1.26 ppm (wet weight). One liver sample had a selenium value in the toxic range for pigs (3.3 ppm wet weight; reference range, 0.4–1.2 ppm). A 1-compartment pharmacokinetic model of selenium elimination in exposed pigs was generated, and the geometric mean blood selenium elimination half-life was estimated to be 12 days. The 60-day withdrawal time recommended by the Food Animal Residue Avoidance Database was considered sufficient to allow safe human consumption of tissues from exposed pigs.

Selenium is an essential trace element for swine, necessary for cells to detoxify peroxides.[29] It is one of the most toxic trace elements[26,33] and has a narrow margin of safety. Toxicosis has been reported in swine after repeated ingestion of feed containing >5 ppm selenium (dry weight).[4,12,24–26] Signs of selenium toxicosis in swine include anorexia, alopecia, separation of hoof and skin at the coronary band, degenerative changes in the liver and kidney, and poliomyelomalacia.[16,26,27,33] In 1974, the US Food and Drug Administration (FDA) authorized the addition of a sodium salt of selenium to swine feed at a concentration of 0.1 ppm (dry weight) in the complete ration.[32] Current FDA regulations allow a maximum of 0.3 ppm (dry weight) in the complete ration as either inorganic sodium selenite or selenate.[7] Sodium selenite is the most commonly used selenium compound in domestic feed because of its lower cost, and it is only available as a feed premix.[32]

Experimental trials describing both the clinical effects and the tissue concentrations of selenium in experimentally intoxicated swine are well documented.[1,2,9–12,14,17,21,23,28,37] Accidental selenium toxicosis in swine has also been widely reported,[13,15,25,30,34–36] but little information is available concerning elimination of selenium from blood and tissues in field outbreaks involving multiple premises and various feed selenium concentrations in affected pigs.

The purpose of this study was to describe clinical, pathologic, and epidemiologic features of an outbreak of selenium toxicosis in 24 swine herds and to monitor selenium elimination from blood and tissues of affected pigs to estimate an appropriate slaughter withdrawal time. The maximum human acceptable intake of selenium has been reported as 500 μg/person/day.[22] Normal selenium values for meat (beef and pork) in the USA have been reported in the range of 0.10–0.40 ppm (wet weight)[22] This study was designed so that meat from the affected pigs would be in the normal range at slaughter.

Materials and methods

Case history. On May 31, 1996, 2 unrelated pigs from San Luis Obispo County exhibiting signs of paralysis were submitted to the California Veterinary Diagnostic Laboratory Service (CVDLS) for necropsy. Histologic lesions and tissue analysis confirmed selenium toxicosis in both pigs. CDVLS notified the California Department of Food and Ag-

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riculture, Animal Health Branch (CDFA-AHB), and an epidemiologic investigation was initiated to determine the source of the toxicosis. The investigation confirmed that the 2 pigs had consumed the same brand of commercial swine feed purchased from a San Luis Obispo feed store. The feed store had received 90 bags of swine feed from a California mill on May 10, 1996.

The trace back to the mill revealed that on May 1, 1996, a mixing error resulted in sodium selenite contamination of 5,425 kg of swine feed. The feed was an 18% protein grower mash, designated for 4-H and Future Farmers of America (FFA) market pigs weighing from 14 to 68 kg. The selenium concentration of the contaminated grower mash was listed as 0.3 ppm (dry weight). A 2% (20,000 ppm, dry weight) sodium selenite premix had been produced the same day, and inadequate system flushing prior to the formulation of the mash was believed to be the cause of the contamination. The 239 22.7-kg bags of mash produced contained various levels of selenium. Two bags were retained by the mill, and the rest were distributed to retail stores located in 7 Southern California counties. The feed company that owned the mill voluntarily recalled the contaminated batch of grower mash on June 5, 1996.

Twenty-four swine herds in San Luis Obispo County with a total of 50 additional pigs had recently purchased grower mash from the implicated feed store. Contaminated feed was identified by date of purchase because identifying lot numbers were not on bags. A feed history questionnaire was given to each herd owner, each pig was clinically examined, and whole blood and feed samples were obtained for selenium analysis. Twenty of the 24 (83.3%) farms had feed from the contaminated batch available for analysis. Feed samples were analyzed for selenium using hydride-generation inductively coupled argon plasma spectometry (ICP).[31] Standard reference materials were utilized, and where appropriate, spiked samples were used. Routine duplicate samples were analyzed to assure precision. The method detection limits were 0.01 ppm for feed analysis and 0.005 ppm for blood and tissue analyses. Additional affected herds were identified in 4 more counties.

A herd was classified as a case herd if 1 or more pigs in the herd had a history of consumption of selenium-contaminated feed. Any pig in a case herd, even if its blood selenium concentration was normal at the time of the first blood test, was considered to have consumed the contaminated feed and was thus designated as exposed. Four herds that had no feed available for analysis owned pigs with elevated blood selenium and had purchased grower mash from the feed store during the week following May 10.

Five exposed pigs exhibiting signs of paralysis from 5 case herds in San Luis Obispo county were subsequently submitted to the CVDLS for necropsy and selenium analysis. Two weeks later, another pig with hind limb ataxia and hoof lesions was submitted from one of these herds. Pigs were euthanized with an overdose of intravenous pentobarbital and necropsied. Tissues were fixed in neutral buffered 10% formalin, embedded in paraffin, sectioned at 6 μm, and stained with hematoxylin and eosin (HE) for histologic examination. Sections of cerebrum, midbrain, medulla, cerebellum, and brain stem and 8–13 sections of spinal cord, sciatic nerve, lung, heart, liver, kidney, spleen, tonsil, skeletal muscle, stomach, small intestine, and colon were examined from each pig. Skin was examined from 3 of the 6 pigs.

Prospective study design. Food Animal Residue Avoidance Database (FARAD) was contacted, and they recommended a 60-day withdrawal time for edible tissues of the exposed pigs. The surviving 44 exposed pigs in 24 San Luis Obispo herds were identified for follow-up to confirm the recommended withdrawal time. Thirty-three pigs (75%) were gilts, and 11 (25%) were barrows; there were 18 (41%) crossbred, 12 (27%) Hampshire, 5 (12%) Landrace, 8 (18%) Yorkshire, and 1 (2%) Poland China. Exposed pigs were followed prospectively to evaluate blood and tissue selenium elimination. Mean weight of pigs at the beginning of follow-up was 49.5 kg (range, 31.8–68.2 kg), and pigs had been eating contaminated feed for a mean of 19 days (range, 5–26 days) prior to initial blood testing.

Exposed pigs were changed to free-choice 17% protein commercial pelleted feed supplied by a single company. The selenium concentration was listed as 0.3 ppm (dry weight), but the single sample tested contained 0.5 ppm (dry weight) of selenium. No additional treatments were administered to the 44 pigs. All 24 herds were on well-water systems with unknown water selenium concentrations and had different housing and management systems.

Blood samples were collected from pigs when first identified as exposed (day 0) and then weekly for approximately 30 days. A final sample was collected a mean of 46 days after the first collection. Initial blood samples of 20 exposed pigs were taken immediately after removal of contaminated feed. The remaining 24 pigs had been removed from contaminated feed a mean of 3 days (range, 1–14 days) prior to the initial blood test. Blood was drawn by jugular venipuncture into ethylenediaminetetraacetic acid tubes, refrigerated, and delivered to CVDLS for selenium analysis within 24 hr of collection. Selenium analysis was performed using ICP.[31]

Twenty-two of the 44 exposed pigs were subsequently exhibited at the local fair and were slaughtered a mean of 72 days after the contaminated feed was removed. Liver and muscle samples were collected at slaughter from these pigs and analyzed for selenium using the ICP technique.

A high school FFA herd of 20 pigs that had been fed a different batch of the implicated company's grower mash was chosen as the control herd. The selenium concentration of the ration fed to control pigs was listed as 0.3 ppm (dry weight). Feed samples obtained at the initial and final blood test dates contained 0.7 ppm (dry weight) and 0.3 ppm (dry weight) of selenium, respectively. Pigs in the control herd were blood tested on the same schedule as the exposed pigs, but no tissue samples were collected at slaughter.

Statistical and pharmacokinetic analyses. Blood selenium concentrations of exposed and control pigs were compared over time in a repeated-measures univariate analysis of variance using a commercial software package.[a] A P value of <0.05 was considered significant.

Blood selenium elimination curves of exposed pigs were fit to a pharmacokinetic model using a commercial software package.[b] After selection of the most appropriate compartmental model, data were analyzed to determine mean blood selenium elimination half-life.

Results

Case investigation. Selenium toxicosis was confirmed in swine herds in 5 of the 7 counties that received contaminated feed. California Department of Food and Agriculture and the feed company identified 120 customers who had purchased feed from the contaminated batch. Almost all of the estimated 150 pigs affected were 4-H or FFA project pigs. One hundred thirty-three (88.7%) of 150 pigs demonstrated either clinical signs of selenium toxicosis or had elevated blood selenium concentrations. Twenty-six affected pigs died statewide.

In San Luis Obispo County, 8 deaths were reported among 52 pigs that consumed contaminated feed. Six affected pigs that were submitted to CVDLS were alert, afebrile, and in sternal or lateral recumbency. All pigs, except 1 pig that had been removed from contaminated feed for 14 days, were still consuming contaminated feed when they died or were euthanized.

Of the 44 surviving exposed pigs in San Luis Obispo County, 33/44 (75%) had clinical signs of selenosis, and 39/44 (88.6%) pigs had elevated (>1 ppm) blood selenium when first tested. Clinical signs in exposed pigs were ameliorated following removal of contaminated feed, and all exposed pigs recovered. The hooves of 2 pigs sloughed, and regrowth took about 30 days. Hair regrowth was complete within 30 days in 17 pigs that had alopecia or rough hair coats. Two pigs that had slight hind limb ataxia also recovered within 30 days. Twenty-two pigs that owners had reported reduced average daily gain returned to normal growth rates within a month.

Gross necropsy findings. The pig surviving the longest had segmented cracks and separation of the hoof wall at the coronary band on the medial, lateral, and frontal aspects of all 4 feet and swelling and thickening of the coronary band. Spinal cord lesions were grossly visible on cut sections of the lumbar cord in 4 pigs and ranged from depressed brown areas with parenchymal collapse dorsoventrally to areas of slight tan discoloration and hemorrhage. One pig had cavitations in the lumbar cord.

Histopathologic findings. All 6 pigs had bilateral symmetrical necrosis of the ventral gray horns (poliomyelomalacia) of the cervical (C6–T1) and lumbar (L4–S1) intumescence. Lesions began in the lateral portion of the ventral horn, which contains the lower motor neurons that innervate the voluntary skeletal muscles of the limbs. In the cervical cord of all 6 pigs and the lumbar cord in 2 of 6 pigs, there was incomplete involvement of the ventral horns. The remaining 4 pigs had some areas of complete destruction of ventral horns and bridging necrosis of the medial gray matter with some destruction of the lower dorsal horns. In all pigs, lesions were more severe in the lumbar cord segments. Large numbers of macrophages filled with necrotic material (gitter cells) infiltrated the necrotic gray matter. Mild inflammatory infiltrates, initially eosinophils and later lymphocytes, were present in response to the necrosis. The pig surviving the longest had loss of neurons and collapse and gliosis of the ventral spinal nerve roots at the affected lumbar and cervical cord regions.

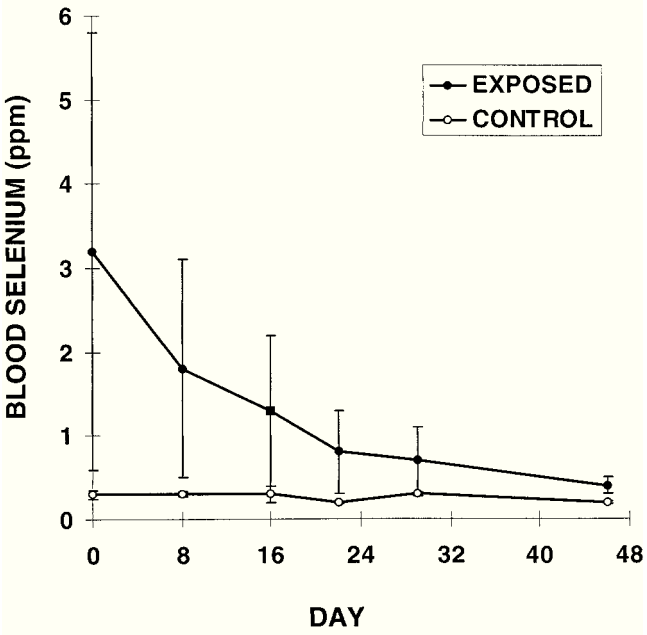

Figure 1. Mean (±SD) blood selenium concentration (ppm) of 44 exposed and 20 control pigs during a 46-day exposure follow-up period. Contaminated feed was withdrawn from exposed pigs a mean of 3 days prior to the first sampling day (day 0). Mean blood selenium concentration of exposed pigs was significantly greater ($P < 0.001$) than that of control pigs at all sampling times.

Feed samples. Feed samples collected from 20 affected herds had a mean selenium concentration of 121.7 ppm (range, 22.1–531 ppm), dry weight.

Prospective study. The mean (±SD) blood selenium concentration of the 44 exposed pigs on the first test (day 0) was 3.2 (±2.6) ppm. After 46 days, the mean concentration was 0.4 (±0.1) ppm. The mean (±SD) blood selenium concentrations of the 20 control pigs on day 0 and day 46 were 0.3 (±0.05) ppm and 0.2 (±0.02) ppm, respectively. Mean blood selenium concentrations of the exposed pigs were significantly higher ($P < 0.001$) than those of the control group at all samplings (Fig. 1).

For generation of the pharmacokinetic curves, a 1 compartment model was chosen as the appropriate model for selenium elimination, because adequate data to depict the initial distribution phase were not available.[8] Five exposed pigs were excluded from analysis because their blood selenium concentrations were <1

Table 1. One-compartment pharmacokinetic model results of blood selenium elimination half-life in pigs exposed to selenium-contaminated feed and in a subset of exposed pigs from which blood samples were obtained immediately after withdrawal of the contaminated feed.

		Elimination half-life (days)	
Herd no.	Pig no.	All exposed pigs	Sampled immediately
1	1	12.6	12.6
	2	14.5	14.5
	3	9.4	9.4
	4	10.1	10.1
2	5	11.7	. . .
	6	8.8	8.8
3	7	8.8	8.8
	8	8.7	8.7
4	9	16.1	16.1
	10	12.8	12.8
5	11	12.7	12.7
6	12	12.2	12.2
	13	8.3	8.3
7	14	25.1	. . .
	15	21.9	. . .
8	16	9.1	9.1
9	17	8.5	8.5
	18	7.6	7.6
10	19	10.6	10.6
	20	11.5	11.5
	21	12.7	12.7
11	22	7.2	7.2
	23	9.3	9.3
12	24	13.7	. . .
	25	10.6	. . .
	26	14.5	. . .
13	28	12.1	. . .
14	30	16.7	. . .
15	32	20.6	. . .
16	33	13.8	. . .
	34	9.8	. . .
17	35	16.6	. . .
	36	11.4	. . .
19	38	14.7	. . .
20	39	11.9	. . .
	40	11.6	. . .
21	41	9.9	. . .
22	42	12.1	. . .
24	44	18.3	. . .
Geometric mean		12.0	10.3

ppm on day 0 (reference range, 0.08–1.0 ppm). Four pigs (7, 19, 21, 28) had two consecutive data points below the control mean of 0.3 ppm, and for these pigs, the last data point was excluded from analysis because the pigs were thought to be no longer eliminating selenium.

When all 39 exposed pigs were included in the model, the geometric mean elimination half-life was 12.0 days (Table 1; Fig. 2a). The geometric mean elimination half-life for the 20 pigs initially sampled immediately after removal of contaminated feed was 10.3 days (Table 1; Fig. 2b).

Tissue samples. Tissues of 22 exposed pigs sampled at slaughter had a mean (±SD) liver selenium concentration of 1.26 (±0.66; range, 0.73–3.32) ppm (wet weight) and a mean (±SD) muscle selenium concentration of 0.36 (±0.05; range, 0.29–0.45) ppm (wet weight). One liver sample had a selenium concentration of 3.3 ppm (wet weight), considered toxic for pigs (reference range, 0.4–1.5 ppm). All muscle samples were within the normal reference range (0.08–0.5 ppm).

Discussion

Distribution of 237 bags of selenium-contaminated feed to herds in 5 affected California counties resulted in one of the more widespread single source outbreaks of selenium toxicosis reported in swine.[13,15,25,30,34–36] The selenium concentrations of the contaminated feed samples recovered in San Luis Obispo County were highly variable (22.1–531 ppm) as was the length of time pigs consumed the feed (5–26 days). Most affected pigs were of similar weight, sex, and age, but housing, water source, and management differed in the 24 case herds that were followed prospectively. However, the clinical presentation, necropsy findings, elimination pattern of blood selenium, and tissue selenium residues found at slaughter were consistent with those aspects of most experimental studies and field investigations of accidental selenium toxicosis.[1,2,4,9–15,17–19,21,23–26,28,30,32–37]

Clinical signs of selenium toxicosis (alopecia, reduced weight gain, hoof lesions) were apparent in 75% of affected pigs and were similar to signs observed in previously described experimental and accidental intoxications.[1,4,9–12,15,23–25,28,30,34–36] Death of 30% (88/300) of feeder pigs accidentally exposed to feed containing a mean of 19 ppm (dry weight) sodium selenite for 42 days was previously reported.[4] In contrast, only 15% (8/52) of the exposed pigs in San Luis Obispo County died in this outbreak. Although the concentration of selenium was higher in this outbreak ($\bar{x}$ = 121.7 ppm), total days on contaminated feed ($\bar{x}$ = 18 days) were less than those reported previously.[4] The lower mortality in the present study may have been in part attributable to the shorter exposure time.

No relationship was evident between the severity of clinical signs and the selenium concentration found in feed or initial blood samples. The pig (no. 13) with the highest initial blood selenium concentration of 12.8 ppm was from herd 6 (feed sample = 115 ppm, dry weight) but showed no overt clinical signs except rough hair coat. In every herd where more than 1 pig consumed contaminated feed, the pig with the most severe clinical signs had lower blood selenium than all other pigs. Anorexia or feed refusal in the severely affected pigs may have caused the blood selenium to decline, as exposure decreased. Feed refusal is often observed when the concentration of selenium in the

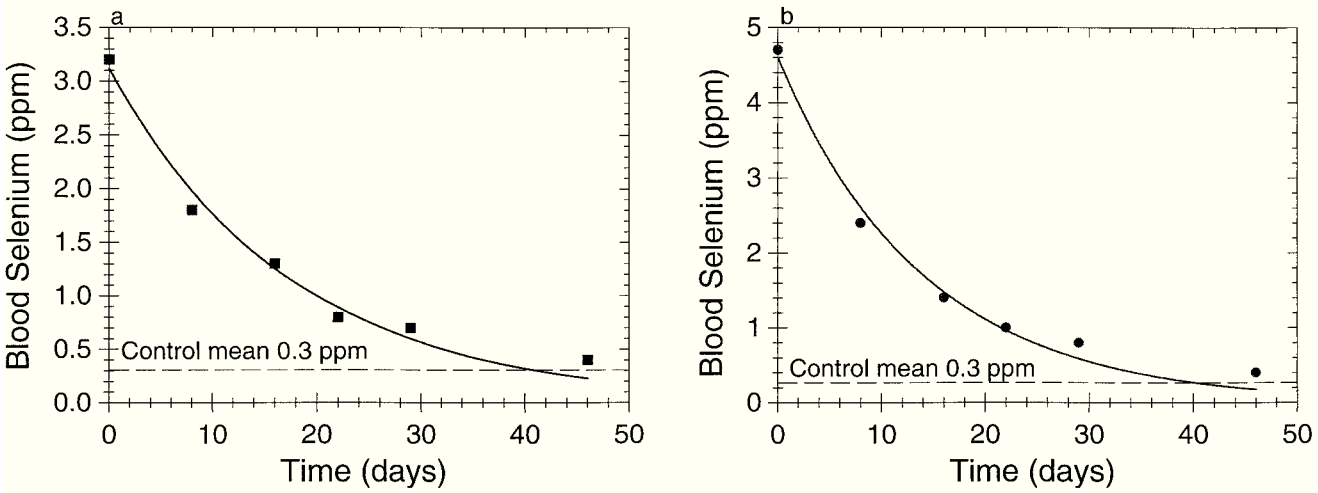

Figure 2. One-compartment model of mean blood selenium elimination curve. **a**. For 39 exposed pigs, elimination half-life was 12 days. **b**. For 20 exposed pigs first sampled immediately after contaminated feed withdrawal, elimination half-life was 10.3 days.

ration exceeds 5 ppm,[1,10,23,24] and variable clinical responses to toxic doses of selenium are common.[36] Although the correlation between selenium concentrations in feed and blood selenium values is well documented,[9,10,37] such a correlation was not found in this outbreak. A recent study has confirmed this finding.[28] Among-pig variation in feed intake, length of time on contaminated feed, and length of time between feed removal and initial blood test may have been factors that contributed to these findings. A relationship between selenium concentration in the feed and blood selenium concentration in the control pigs did exist, similar to that in previous reports.[9,10,37]

Gross and histopathologic changes in the spinal cord were compatible with previously reported lesions due to selenium toxicosis in pigs.[13,14,28,35,36]

A 1-compartment pharmacokinetic model was chosen to depict blood selenium elimination. Although the lack of data immediately after exposure makes a description of the initial distribution phase of blood selenium impossible, the weekly blood samples provided adequate data to approximate blood selenium elimination half-life under field conditions.[8] The log dose–response curves were curvilinear for all pigs modeled. Sheep given intravenous bolus toxic doses of sodium selenite and evaluated for 8 days postdosing showed triphasic elimination curves, resulting in a biological half-life of 14.7 days.[3] In the present study, pigs that received repeated oral toxic doses of sodium selenite had a biological half-life of selenium of 12 days.

The purpose of the prospective study was to evaluate selenium elimination during the 60-day withdrawal time recommended by the FARAD and to determine if exposed pigs would reach normal (<1 ppm) blood selenium concentrations 60 days after feed withdrawal to allow slaughter for human consumption. Mean blood selenium concentration of exposed pigs on day 46 was 0.4 ppm (Fig. 1), and a simulated pharmacokinetic model indicated that all pigs would have blood selenium concentrations similar to control pigs by day 60.

Because blood and tissue selenium concentrations have been shown to have a high correlation with dietary intake of selenium,[2,9,11,17–19,21,37] blood selenium concentrations after 60 days should approximate muscle selenium concentrations. Mean blood selenium concentration of exposed pigs on day 46 was 0.4 ppm (Fig. 1), and model simulation estimated that by day 60 the mean blood concentration would decrease to 0.3 ppm. Mean muscle selenium concentrations of the 22/44 exposed pigs sampled at slaughter (72 days after contaminated feed was withdrawn) was 0.36 ppm (wet weight). In this study, mean blood selenium concentrations would have approximated mean muscle concentrations by day 60. Initial muscle selenium concentrations were unknown for the pigs monitored in the prospective study, but 60 days appeared to be an adequate withdrawal time for the elimination of toxic concentrations of selenium that may have accumulated in muscle.

At slaughter, 1 pig (no. 7) had liver selenium concentrations in the toxic range (>3 ppm wet weight). In cases of chronic selenium toxicosis in swine where high concentrations of sodium selenite have been the cause, liver has been shown to be the organ with the highest concentration of selenium.[9,21,23,24]

Although 1 liver had elevated selenium 72 days after withdrawal of contaminated feed, it is unlikely that there would have been a food safety risk to human beings. Daily dietary recommendations for selenium vary from 40 μg/person/day,[20,22] which is a recommended daily allowance of 0.87 μg/kg/day[6] (70 μg for a 79-kg person), to a maximum acceptable intake of 500 μg/person/day.[22] For cancer chemoprevention, a

dose of 750–4,990 μg/day has been suggested.[5] Consumption of 150 g of the liver of pig 7 would have provided 495 μg of selenium.

Results of this study indicate that in this outbreak of selenium toxicosis with variable and extremely high concentrations of selenium fed for different periods of time, a 60-day withdrawal time was appropriate to allow both blood and muscle selenium to decrease to reference ranges. Special consideration should be given to organ meats because a high selenium concentration was detected in 1 liver.

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Sources and manufacturers

a. BMDP 7.0 (1992), BMDP Statistical Software, Los Angeles, CA.
b. PK Analyst 1.0 (1995), Micromath Scientific Software, Salt Lake City, UT.

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