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Assessment of some toxic elements (Co, Cr, Mn, Se, and As) in muscle, offal, hair, and blood of camels (*Camelus dromedaries*) and their risk assessment

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Abstract

Background: Camel meat tainted with heavy metals or trace elements may pose a health risk to consumers. Heavy metal contamination poses a severe danger due to both their toxicity and bioaccumulation in the food chain.

Aim: To estimate the residual levels of heavy metals (Co, Cr, Mn, Se, and As) in muscle, liver, kidney, hair, and serum of three camel breeds (Magaheem, Maghateer, and Wadha) collected from Al-Omran abattoir, Al-Ahsa, Saudi Arabia.

Methods: A total of 225 tissue samples (muscles, liver, kidney, serum, and hair) were taken and analyzed using an Atomic Absorption Spectrophotometer. Health risk assessment was assessed using the guidelines set by the US Environmental Protection Agency.

Results: Camel breed significantly ($p < 0.05$) influences Co, Cr, Mn, and Se accumulation and distribution in organs and muscle; however, arsenic accumulation was not significantly affected ($p < 0.05$) by camel breeds. The highest values of Co, Cr, Se, and Mn in all examined samples were detected in the liver samples of Maghateer and Magaheem breeds. Furthermore, significant strong positive correlation between serum and liver cobalt, chromium, manganese, and arsenic. The estimated daily intake owing to camel meat consumption was less than the tolerated daily intake.

Conclusion: Heavy metals were distributed among different breeds of camel. Trace elements (Pb and Cd) in meat and offal were below the international maximum permissible limit. The correlation between samples reflects the role of hair as a good tool for the identification of heavy metal pollution.

Keywords: Camel carcass, Toxic metals, Risk assessment.

Introduction

Saudi Arabia is the Middle East's largest producer of camel meat, accounting for 62% of the total volume with annual per capita consumption of 3.10 kg (Index box, 2022). Camel meat is becoming increasingly popular due to its low fat, low cholesterol, and high polyunsaturated fatty acids (Kadim *et al.*, 2008). Because of its comparable nutritional value, camel meat is a good alternative to other red meat (Kadim *et al.*, 2022). The hazard of heavy metals in meat is of big concern for food safety and public health as well due to their toxic effect at very low concentrations (Santhi *et al.*, 2008). When camels graze freely and drink water from contaminated sources, heavy metals may bio-accumulate and bio-magnify in their tissues and organs (Bala *et al.*, 2018).

Some heavy metals were proven to have carcinogenic, mutagenic, or teratogenic effects (Pitot and Dragon, 1995). In addition, toxic metals may compromise the metabolism and bioavailability of essential metals and decrease their body concentration (Lazarus, 2010; Matović *et al.*, 2011). Trace elements, such as selenium, manganese, and cobalt, are essential metals where they play a significant role in biological systems. However,

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they can be very harmful and produce toxic effects if taken in excessive amounts (Mohammed *et al.*, 2011).

Chronic arsenic toxicity increases the risk of developing various cancers, such as skin, liver, lung, bladder, kidney, and colon cancer (Hu, 2002).

Manganese toxicity can cause many pathological alterations in the CNS, reproductive and immune system dysfunction, damage to the testicles and pancreas, and hepatitis (Keen and Leach, 1987). Selenium plays a significant role in the health of both animals and humans. It is a crucial component of several enzymes that are required for the immune system as well as anti-carcinogenic activity (Navarro and Lopez, 2000).

Monitoring the levels of trace elements and heavy metals in camel meat, as a human food, is of significant importance for both food safety and human health. Therefore, the goal of this research is to assess the levels of trace elements (selenium, manganese, and cobalt) and heavy metals (arsenic and chromium) in the blood, hair, and offal of three different camel breeds (Magaheem, Maghateer, and Wadha) in Al-Ahsa province, Saudi Arabia. In addition, human dietary intake of these metals and risk assessment associated with the consumption of such camel meat were estimated.

Materials and Methods

Samples collection

A total of 225 tissue samples of muscles, liver, kidney, serum, and hair ($n = 45$ for each) were taken from three local camel breeds directly after slaughter. Samples were obtained from Al-Omran central slaughterhouse, Al-Ahsa, Saudi Arabia.

Al-Ahsa is classified as rural since it relies primarily on livestock production, but industrial activities are restricted. From October 2021 until January 2022, samples were gathered. The ages of the animals ranged from less than 5 to more than 10 years. All animals appeared to be in good health, active and disease-free. The samples were kept at a temperature of −20°C in falcon tubes until analysis.

Sample preparation and extraction

The Shimadzu AA-7000 Atomic Absorption Spectrophotometer was used in conjunction with a graphite furnace atomic absorption spectrometry system (GFAAS) to assess the amounts of the trace elements (Se, Mn, Cr, Co, and As) (Table 1). In addition, hollow cathode lamps were used for the analysis. For Se, Mn, Cr, Co, and As analysis, were measured using the GFAAS system. The Shimadzu ASO6100 Automatic Sampler was used to inject the samples into the GFAAS (Waheed *et al.*, 2022). After dilution and filtration with Whatman filter paper 1, the digested samples were analyzed using atomic absorption spectrophotometry according to the method mentioned by Meligy *et al.* (2019) and Hussein *et al.* (2022). Metal concentrations were calculated using standard curves for all metals studied.

Quality assurance and control

Measurement of IAEA142/TM from IAEA-certified reference materials (muscle homogenate) was used to ensure the accuracy of the assay (Vienna, Austria). The certified samples' recovered concentrations were 5% of the certified values. Triplicates of each sample were evaluated.

Estimated daily intake (EDI)

As described by the Human Health Evaluation Manual (United States Environmental Protection Agency, 2002), the equation was used to calculate the EDI of the metals studied: $EDI = Cm \times FIR/BW$. Where EDI is expressed in µg/kg/day; Cm is the metal concentration in the sample (measured in mg/kg wet weight); FIR is for Saudi Arabia's meat intake rate, which was assessed to be 146 g per day; BW stands for Saudi adults and children body weight, which was assessed to be 70 kg for adults and 30 kg for children (Adam *et al.*, 2014, Hussein *et al.*, 2022).

Health risk assessment

The noncancer risk caused by the consumption of metal-contaminated edible tissues by the Saudi population (adults and children) was assessed using the guidelines set by the (United States Environmental Protection Agency, 2002).

Statistical analysis

SPSS (2010) was utilized to conduct statistical analysis. To see if variables were normally distributed, the Kolmogorov-Smirnov normality test was used. One-way analysis of variance was applied to compare the means of the groups when breed was used as a factor. To examine the impact of breed on the analyzed parameters, the Duncan multiple range test (Steel and Torrie, 1980) was used. The differences between genders were tested by independent *t*-test.

Table 1. Recovery of trace elements and heavy metals from homogeneous muscle samples.

Elements	Concentration of metal added (µg/g)	Concentration of metal recovered (µg/g)	Recovery (%)
Selenium (Se)	3	2.80	93.3
Cobalt (Co)	3	2.75	91.6
Arsenic (As)	3	2.70	90.0
Manganese (Mn)	3	2.90	96.6
Chromium (Cr)	3	2.85	95.0

Ethical approval

All research procedures were carried out by King Faisal University's regulations and requirements.

Results

Cobalt

The recorded data in Figure 1A declared that mean values of Cobalt ranged from 0.246 to 1.03, 0.024 to 0.652, 0.004 to 0.043, 0.008 to 0.066, and 0.205 to 0.326 mg.kg^{-1} in liver, kidney, muscle, serum, and hair, respectively. The cobalt values significantly varied between breeds ($p < 0.05$). Furthermore, values are arranged in a descending manner liver > kidney> hair > serum > muscle.

Regarding the effect of gender as shown in Figure 1B, all male collected samples had substantially greater ($p < 0.05$) Co levels than female samples. The correlation coefficient between Co concentrations in organs and serum with breed and gender in Table 2 revealed a strong positive correlation between muscle and liver cobalt levels.

Chromium

The recorded data in Figure 2A declared that mean values of chromium ranged from 0.41 to 0.75, 0.23 to 0.57, 0.02 to 0.20, 0.12 to 0.41, and 0.05 to 0.95 mg.kg^{-1} in liver, kidney, muscle, serum, and hair, respectively. Furthermore, values are arranged in a descending manner hair > liver > kidney > serum > muscle. The chromium content in all male samples studied was considerably greater ($p < 0.001$) than in female samples (Fig. 2B).

Manganese (Mn)

The recorded data in Figure 3A declared that mean values of Mn ranged from 0.460 to 1.6, 0.310 to 1.5, 0.000 to 0.690, 0.41 to 0.77, and 3.06 to 5.761 mg.kg^{-1} in liver, kidney, muscle, serum, and hair, respectively. The Mn content in all male camel samples studied was considerably greater ($p < 0.001$) than in female camel samples (Fig. 3B).

Selenium

The recorded data in Figure 4A declared that mean values of selenium ranged from 0.424 to 0.424, 0.28 to 0.76, 0.211 to 0.587, 0.156 to 0.367, and 0.11 to 0.589 mg.kg^{-1} in liver, kidney, muscle, serum, and hair, respectively. The selenium content in all male camel samples studied was considerably greater ($p < 0.05$) than in female samples (Fig. 4B). The correlation coefficient between Se concentrations in organs and serum with breed and gender in Table 5 revealed a strong positive correlation between muscle and kidney cobalt level. Moreover, a positive correlation was detected between serum, liver, kidney, and hair.

Arsenic

The obtained data in Figure 5A declared that mean values of As ranged from 0.304 to 0.887, 0.224 to 0.723, 0.15 to 0.44, 0.12 to 0.37, and 0.02 to 0.27 mg.kg^{-1} in liver, kidney, hair, muscle, and serum, respectively. The correlation coefficient between As concentrations

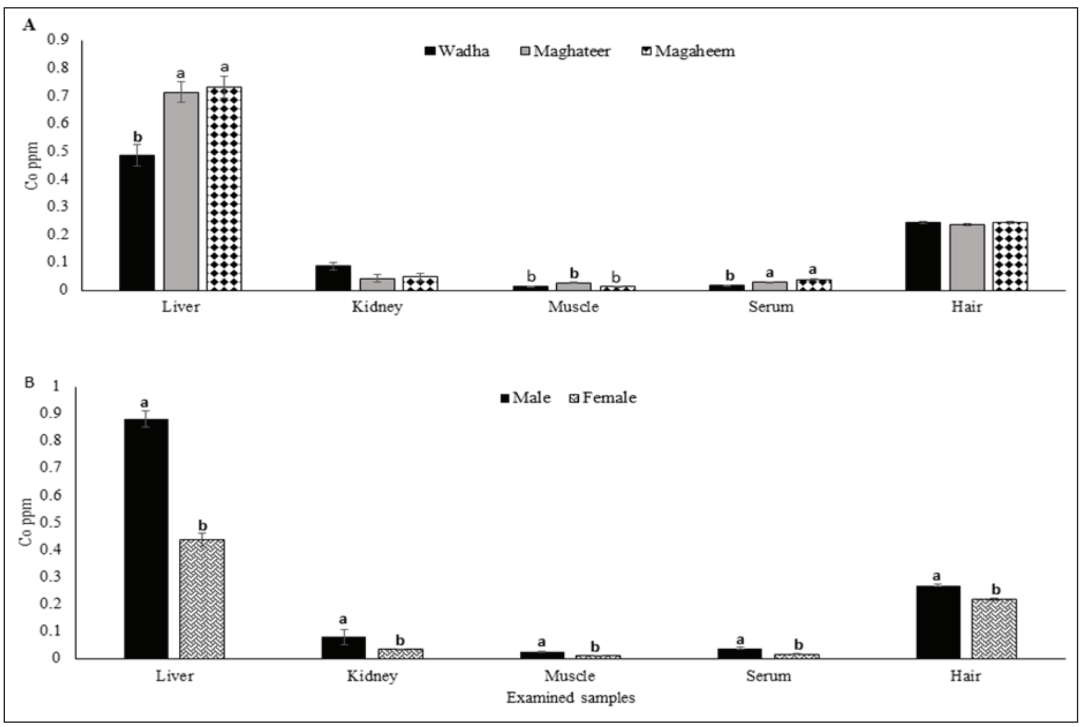

Fig. 1. Cobalt mean values (ppm) in liver, kidney, muscle, serum, and hair A. Effect of breed on cobalt concentrations (ppm). B. Effect of Gender on cobalt concentration (ppm). [a,b] Means with different superscript letters in the same sample type are significantly different ($p \leq 0.05$).

Table 2. Correlations between cobalt concentrations in organs and serum with breed and gender.

Cobalt	Breed	Gender	Liver	Kidney	Muscle	Serum	Hair
Breed		0.000	0.401**	−0.18*	−0.44	0.541**	0.025**
Gender	0.000		−0.876**	−0.29*	−0.670**	−0.697**	−0.82**
Liver	0.401**	−0.876**		0.133	0.699**	0.826**	0.699**
Kidney	−0.18*	−0.29*	0.133		0.107	0.096	0.182
Muscle	−0.44	−0.67**	0.699**	0.107		0.486**	0.388**
Serum	0.541**	−0.697**	0.826**	0.096	0.486**		0.56**
Hair	0.025**	−0.821**	0.699**	0.182	0.388**	0.56**	

(**) Correlation is significant at the 0.01 level. (*) Correlation is significant at the 0.05 level. Values presented in the table are correlation coefficient.

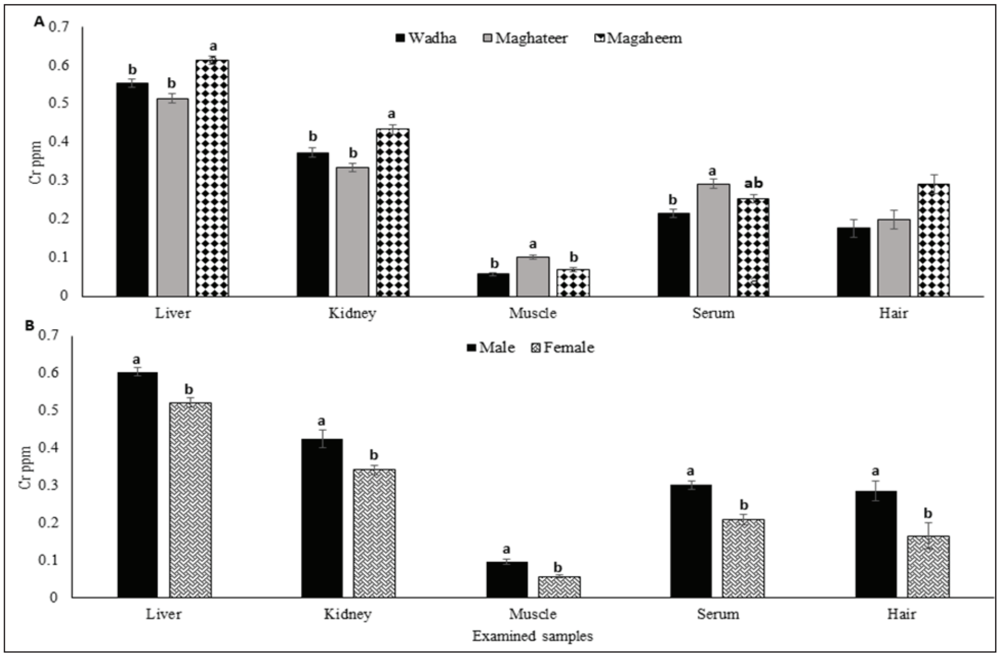

Fig. 2. Chromium mean values (ppm) in liver, kidney, muscle, serum, and hair A. Effect of breed on chromium concentrations (ppm). B. Effect of Gender on chromium concentration (ppm). [a,b] Means with different superscript letters in the same sample type are significantly different ($p \leq 0.05$).

in organs and serum with breed and gender in Table 6 revealed a strong positive correlation between gender and all examined samples (Fig. 5B). Meanwhile, breeds negatively correlated with liver, kidney, and hair.

Health risk assessment

The presented results in Table 7 indicated that the EDI of all investigated metals from all breeds were below the tolerated daily intake (TDI) approved by FAO/WHO (2010). The noncarcinogenic hazard ratios (HRs) and hazard indices (HIs) were assessed in Table 8.

Discussion

Cobalt

The maximum Co concentration found in liver samples from different camel breeds was equivalent to the finding of Mahmud *et al.* (2011) and Asli *et al.* (2020) who examined muscle and liver in Iranian camels and found low concentrations in the liver and muscle of camels. Relatively higher levels of Co were reported in the liver compared with meat, liver, lung, heart, and kidney in previous studies as 1.10–14.22 mg kg^{-1} (Chafik *et al.*, 2014) and 1.913–8.194 mg kg^{-1} (Al-Perkhdri, 2021).

Camel breed influences Co accumulation and distribution in camel organs and muscle. Significant variations ($p < 0.05$) were found across breeds, which can be explained by each breed's environment being in a distinct geographical location with varying concentrations of metals in soil, forages, and water. Faye *et al.* (2008) detected significantly higher cobalt

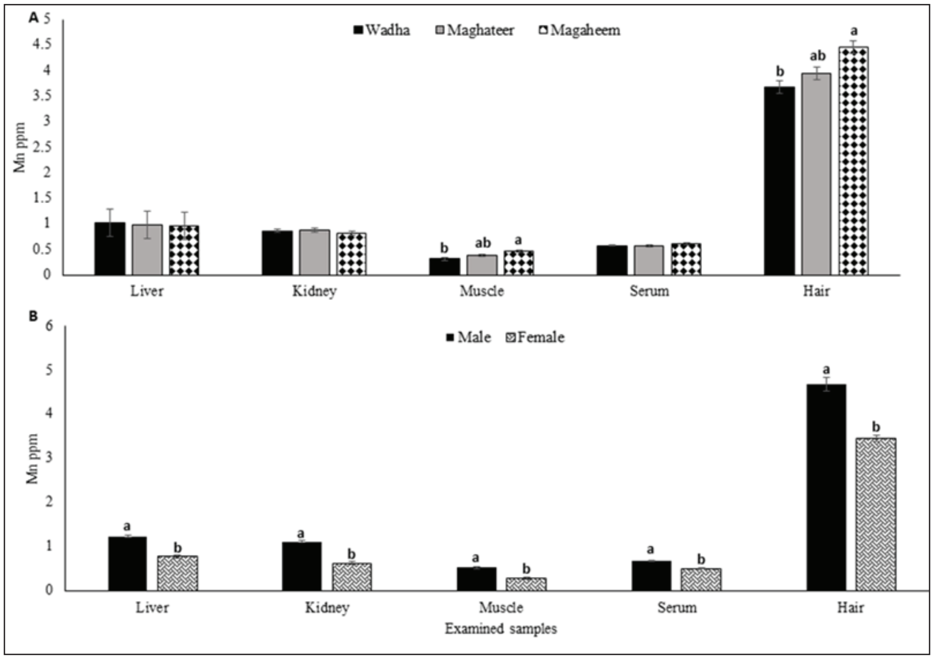

Fig. 3. Manganese mean values (ppm) in liver, kidney, muscle, serum, and hair A. Effect of breed on manganese concentrations (ppm). B. Effect of Gender on manganese concentration (ppm). [a,b] Means with different superscript letters in the same sample type are significantly different ($p \leq 0.05$).

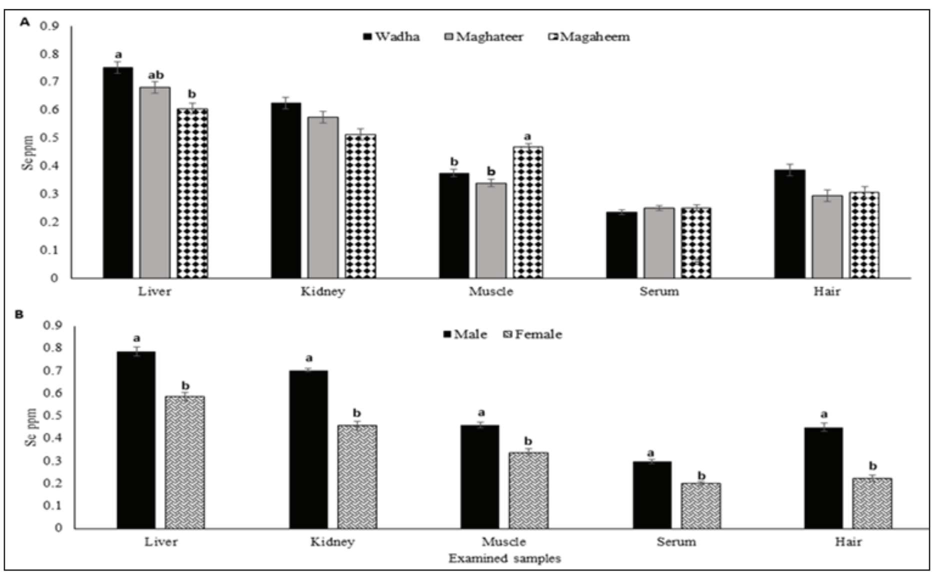

Fig. 4. Selenium mean values (ppm) in liver, kidney, muscle, serum, and hair A. Effect of breed on selenium concentrations (ppm). B. Effect of Gender on selenium concentration (ppm). [a,b] Means with different superscript letters in the same sample type are significantly different ($p \leq 0.05$).

levels in male than female camels collected from Emirates. The positive correlation attributed to Co can enter the body through the digestive tract from food or drink water or lungs after inhalation of Co dust.

Chromium

The chromium concentration in the current study ranged from 0.032 to 96.62 mg/kg. There are significant differences ($p < 0.05$) between breeds according to their contents of Cr between liver kidney, muscle, and hair (Fig. 2A). The Cr variations in our findings are attributable to variances in the availability of Cr in forages that are grown in the grazing areas. The highest values of Cr in all examined samples were detected in the liver samples of maghateer magaheem breeds.

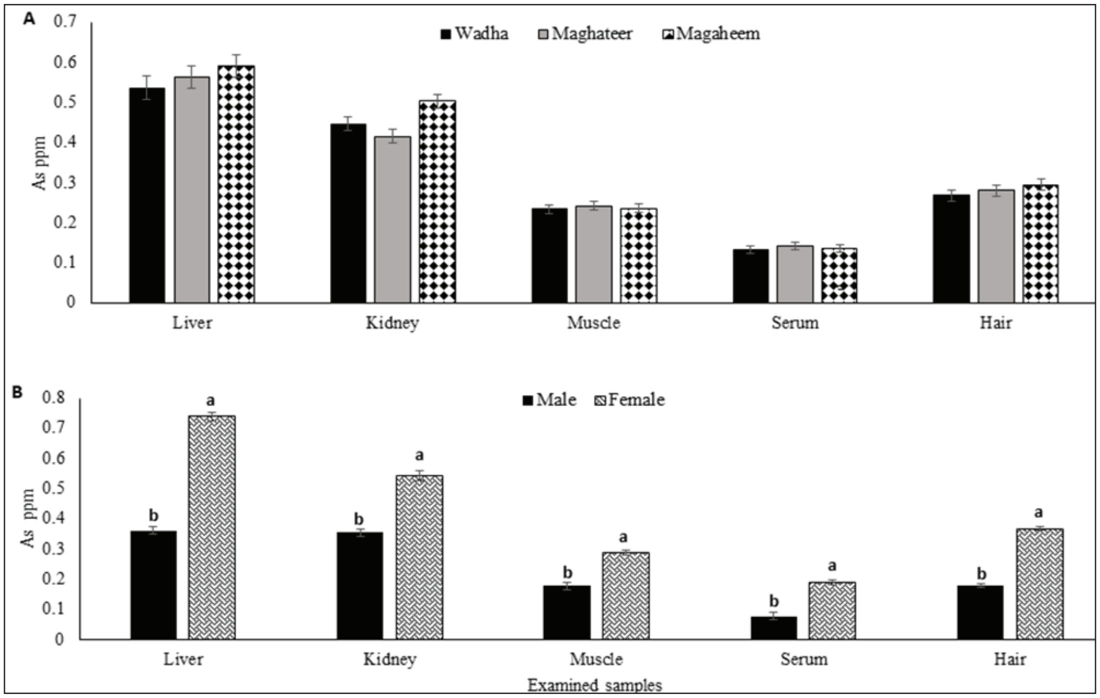

Fig. 5. Arsenic mean values (ppm) in liver, kidney, muscle, serum, and hair A. Effect of breed on arsenic concentrations (ppm). B. Effect of gender on arsenic concentration (ppm). [a,b] Means with different superscript letters in the same sample type are significantly different ($p \leq 0.05$).

Table 3. Correlations between chromium concentrations in organs and serum with breed and gender.

Iron	Breed	Gender	Liver	Kidney	Muscle	Serum	Hair
Breed		0.000	0.351*	0.351*	0.132	0.195	0.297*
Gender	0.000		−0.591**	−0.591**	−0.558**	−0.587**	−0.382**
Liver	0.351*	−0.591**		1.00	0.195	0.297**	0.259
Kidney	0.351*	0.591**	1.00**		0.195	0.297**	0.259
Muscle	0.132	−0.558**	0.195	0.195		0.527**	0.179
Serum	0.195	−0.587**	0.297*	0.297*	0.527**		0.06
Hair	0.297*	−0.382**	0.259	0.259	0.179	0.063	

(**) Correlation is significant at the 0.01 level. (*) Correlation is significant at the 0.05 level. Values presented in the table are correlation coefficient based on Pearson Correlation coefficients.

Table 4. Correlations between manganese concentrations in organs and serum with breed and gender.

Copper	Breed	Gender	Liver	Kidney	Muscle	Serum	Hair
Breed		0.000	−0.082	−0.086	0.422**	0.128	0.389**
Gender	0.000		−0.862**	−0.875**	−0.775**	−0.833**	−0.736**
Liver	−0.085	−0.862		0.992**	0.690**	0.772**	0.698**
Kidney	−0.086	−0.875**	0.992		0.680**	0.775**	0.693**
Muscle	0.422**	−0.775**	0.690**	0.68**		0.737**	0.757**
Serum	0.128	−0.833**	−0.772**	0.775**	0.737**		0.706**
Hair	0.389**	−0.763**	0.698**	0.693**	0.693**	0.706**	

(**) Correlation is significant at the 0.01 level (2-tailed).

Table 5. Correlations between selenium concentrations in organs and serum with breed and gender.

Lead	Breed	Gender	Liver	Kidney	Muscle	Serum	Hair
Breed		0.000	−0.452**	−0.318	0.416**	0.103	−0.239
Gender	0.000		−0.745**	0.86**	−0.673**	−0.804**	−0.818**
Liver	−0.456*	−0.745**		0.745**	0.257	0.584**	0.662**
Kidney	−0.318*	−0.86**	−0.745**		0.464**	0.665**	0.809**
Muscle	0.416 **	−0.673**	0.257	0.464**		0.501**	0.497**
Serum	0.103	−0.804**	0.584**	0.665**	0.501**		0.593**
Hair	−0.239	−0.818**	0.662**	0.809**	0.497**	0.593**	

(**) Correlation is significant at the 0.01 level (2-tailed). (*): Correlation is significant at the 0.05 level (2-tailed).

Table 6. Correlations between arsenic concentrations in organs and serum with breed and gender.

Lead	Breed	Gender	Liver	Kidney	Muscle	Serum	Hair
Breed		0.000	0.115	0.197	0.011	0.011	0.115
Gender	0.000		0.954**	0.793**	0.773**	0.773**	0.954**
Liver	0.115	0.954**		0.810**	0.746**	0.746**	1.000**
Kidney	0.197	0.793**	0.810**		0.697**	0.697**	0.810**
Muscle	0.011	0.773**	0.746**	0.697**		1.000**	0.746**
Serum	0.011	0.773**	0.75**	0.697**	1.000**		0.746**
Hair	0.115	0.954**	1.000**	0.810**	0.746**	0.746**	

(**) Correlation is significant at the 0.01 level (2-tailed)

The correlations between chromium concentrations in organs and serum with breed and gender was displayed in Table (3). The average of Cr in this study was (0.4) mg/kg in meat and organs which coincided with USDA (2006) and China standards (2006) which stated the maximum level of chromium in meat as 1.0 mg/kg. Higher Cr values obtained were 2.333–4.92 mg kg^{-1} of muscle and 4.256–9.878 mg kg^{-1} of liver samples in Iran (Asli *et al.*, 2020).

Manganese (Mn)

Manganese values significantly varied between breeds ($p < 0.05$). Furthermore, values are arranged in a descending manner hair > liver > kidney > serum > muscle. The Mn content in all male camel samples studied was considerably greater ($p < 0.001$) than in female camel samples (Fig. 3B). Similar to our finding male and female camels had Mn in hair (Faraz *et al.*, 2020). In addition, adult male and female camel from Pakistan dromedary calves contained 45.8 ± 1.8 and 32.9 ± 4.4 ppm in male and female hair, respectively (Faraz *et al.*, 2020). On the other hand, there were significant variations ($p < 0.05$) between Mn content in collected meat samples from middle and southern districts and other districts in the Saudi Kingdom (Faraz *et al.*, 2020). The correlation coefficient between Mn concentrations in organs and serum with breed and gender in Table 4 revealed a strong positive correlation between muscle and hair Mn levels. Moreover, a positive correlation was detected between serum and liver. The negative correlation obtained for both breed and gender may attributed to the accumulation of heavy metals in the animal body related to environmental factors such as air pollution, feeding, and available water sources.

Selenium

The Se values significantly varied between breeds ($p < 0.05$). Furthermore, values are arranged in a descending manner kidney > hair > muscle > liver > serum. The current findings of higher values of Se in kidney samples come in accordance with Seboussi *et al.* (2010) reported the selenium concentrations in liver (216.1 µg/kg), kidney (1,006 µg/kg), for limb muscle (368.7 µg/kg), and hair (80.7 µg/kg). It is proved that the kidney was the richest organ in Se. In addition, the hair seemed to be the best indicator of selenium intake in camel (Seboussi *et al.*, 2010). In Saudi Arabia, serum Se values reported in young camels at the slaughterhouse varied between 5.3 and 131 ng/ml. Serum concentrations in camels were 0.281 ppm on average in sera coming from the Sultanate of Oman (Faye *et al.*, 2008). The threshold for serum selenium to be considered a deficiency is below 35 ng/ml as indicated by El-Khouly *et al.* (2001). However, in young adults, Al-Qarawi *et al.* (2001) reported the appearance of clinical signs of Se deficiency only in animals with selenium values below 5 ng/ml. The selenium content in all male camel samples studied was considerably greater ($p < 0.05$) than in female samples (Fig. 4B). Meanwhile, Seboussi *et al.* (2004) recorded that adult males presented lower values than females 139 ± 5 versus 229 ± 7 ng/ml, respectively.

Table 7. EDI in comparison with TDI (µg/kg/day) due to ingestion of camel meat from different breeds.

	Breed	Cobalt	Chromium	Manganese	Selenium	Arsenic
EDI Adult	Wadha	0.029	0.121	0.653	0.784	0.490
	Maghateer	0.055	0.214	0.811	0.711	0.507
	Magaheem	0.027	0.145	0.984	0.979	0.492
EDI Child	Wadha	0.069	0.282	1.524	1.830	1.144
	Maghateer	0.127	0.501	1.896	1.660	1.183
	Magaheem	0.064	0.336	2.297	2.282	1.149
TDI µg/kg/day		120	300	428.57	6.67	2.14

(TDI): Tolerable daily intake according to FAO/WHO (2010).

Table 8. The HR and HIs are due to ingestion of camel meat from different breeds.

		HR (Co)	HR (Cr)	HR (Mn)	HR (Se)	HIs (∑ HRi) without arsenic	HR (As)	HIs (∑ HRi) with arsenic
HR Adult	Wadha	0.097	0.040	0.005	0.157	0.299	1.634	1.933
	Maghateer	0.180	0.072	0.006	0.142	0.4	1.689	2.089
	Magaheem	0.090	0.048	0.007	0.196	0.341	1.641	1.982
HR Child	Wadha	0.227	0.094	0.011	0.366	0.698	3.812	4.51
	Maghateer	0.421	0. 167	0.014	0.332	0.767	3.942	4.709
	Magaheem	0.210	0. 112	0.016	0.456	0.682	3.828	4.51

The correlation coefficient between Se concentrations in organs and serum with breed and gender in Table 5 revealed a strong positive correlation between muscle and kidney cobalt levels. Moreover, a positive correlation was detected between serum, liver, kidney, and hair. The negative correlation obtained for both breed and gender may attributed to the accumulation of trace elements in the animal body related to environmental factors. The highest values for Se were detected in the Wadha breed than the other two breeds. There was a contradiction in the breed effect when compared to the work done by Abdelrahman *et al.* (2013), who reported a two-fold higher concentration in Majaheem camels (147.1 ng/ml) than in Waddha camels (73.3 ng/ml), while Seboussi *et al.* (2004) indicated no genetic difference.

Arsenic

The As values were not significantly varied between breeds but were highly significant with the effect of Gender. The obtained results were in comparable with the findings of El-Ghareeb *et al.* (2019). One probable explanation for the high As level in the studied samples is the use of feed additives rich in arsenic during intensive production, which is common in several regions worldwide (Hu *et al.*, 2017). Inorganic arsenic is naturally present at high levels in the groundwater of a number of countries. Sources of arsenic exposure could include drinking water, crops irrigated with such water, and food produced with such water as well (Flanagan *et al.*, 2012). The correlation coefficient between As concentrations in organs and serum with breed and gender in Table 5 revealed a strong positive correlation between gender and all examined samples. Meanwhile, breeds negatively correlated with liver, kidney, and hair.

Health risk assessment

The presented results in Table 7 indicated that the EDI of all investigated metals from all breeds were below the TDI approved by FAO/WHO. The EDI of Pb and Cd were lower than those reported from camel meat in Saudi Arabia (El-Ghareeb *et al.*, 2019). The noncarcinogenic HRs and HIs were assessed in this study in Table 8. The HR from all examined metals below 1 meanwhile, HR(As) exceeding 1 for adults and children as 1.634 and 3.812, 1.689 and 3.942, and 1.641 and 3.828 from meat consumption of Wadha, Maghateer, Magaheem breeds, respectively. Since the toxicological profile primarily takes into account the inorganic chemical forms of arsenic, HR values for As bigger than one are not relevant for human wellness. This is because organic forms of arsenic are relatively nontoxic to humans (ATSDR, 2005). The HIs due to the consumption of the Maghateer breed are slightly higher than Wadha or Magaheem. On neglecting HR (As), HIs values were below 1, which proved no potential exposure to risk due to the consumption of camel meat from different breeds. The obtained values for HR and HIs were lower than those in Ghana (Bortey *et al.*, 2015) and Saudi Arabia (El-Ghareeb *et al.*, 2019).

Conclusion

It can be concluded that heavy metals are distributed among camel samples of different breeds. Trace elements (Pb and Cd) in meat and offal were below the international maximum permissible limit. The correlation between samples reflects the role of hair as a good tool for the identification of heavy metal pollution. In addition, no potential health hazards among camel meat consumers in Saudi Arabia especially, adults. We need some future studies to differentiate between the percentages of organic and inorganic arsenic in camel meat and offal.

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Conflict of interest

The authors declare that there is no conflict of interest.

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The Annual Funding track by the Deanship of Scientific Research, Vice Presidency for Graduate Studies and Scientific Research, King Faisal University, Saudi Arabia [Project No. 4002].

Data availability

All data are provided in the manuscript. Any extra data needed can be provided by the corresponding author upon reasonable request.

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