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ARTICLE

Analysis of Perchlorate in Milk Powder and Milk by Hydrophilic Interaction Chromatography Combined with Tandem Mass Spectrometry

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A simple, selective, and sensitive method using hydrophilic interaction chromatography combined with tandem mass spectrometry (HILIC−MS/MS) for quantifying perchlorate in milk powder and milk was developed. The analysis was conducted on an Inertsil HILIC column (150 mm × 3.0 mm, 3.5 μm) using a mobile phase consisting of methanol and 0.1% formic acid (60:40, v/v). The detection was performed by MS/MS via electrospray ionization. Linear calibration curves were obtained in the concentration range of 2.00×10^{-2} to 8.00 μg/g and 4.00×10^{-1} to 20.0 μg/L for perchlorate in milk powder and milk, respectively. The method detection limit was 4.00×10^{-3} μg/g for milk powder and 8.00×10^{-2} μg/L for milk. The recoveries of perchlorate in milk powder and milk were all >90%. This method was successfully applied to the quantitative determination of perchlorate in milk powder and milk.

KEYWORDS: HILIC−MS/MS; perchlorate; milk powder; milk; ESI

INTRODUCTION

As an oxidant, perchlorate has been widely used in the production of rocket fuel, missiles, flares, and fireworks since the 1940s. A recent study has shown the existence of natural perchlorate in sodium nitrate deposits in Chile. Perchlorate is highly soluble and stable in water and persists for many decades (*1*). Perchlorate has been detected in surface water, groundwater, and drinking water throughout the United States (*2*). Food crops can absorb and concentrate perchlorate (*3*−*5*). Milk may also contain perchlorate, possibly from the cow feeding on perchlorate-contaminated water or foods (*6*, *7*). Perchlorate has long been known to competitively inhibit normal iodide uptake by the human thyroid gland. For many years, perchlorate was used in the treatment of hyperthyroidism, the overproduction of the iodine-containing hormones triiodothyronine (T_3) and thyroxine (T_4). Perchlorate has the potential to cause hypothyroidism in humans because of the reduction of T_3 and T_4, both of which are critical for normal growth and cognitive development in fetuses, newborns, and young children (*8*). The National Academy of Sciences listed the fetal and neonatal life stages as most susceptible to potential perchlorate toxicity because they may be more sensitive to thyroid perturbations and may have higher perchlorate exposure (*9*). It is crutial that a sensitive and selective method for analysis of perchlorate in milk powder, milk, and breast milk be developed.

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Various methods, including UV−vis spectrophotometry (*10*−*12*), Fourier transform infrared spectrometry (*13*), Raman spectroscopy (*14*), ion-selective electrodes (*15*), and capillary electrophoresis (*16*), have been applied in analyzing perchlorate. Ion chromatography with conductivity detection (IC-CD) is the most widely used technique for the determination of perchlorate and typically has reporting limits of 4 μg/L (EPA Methods 300.1 and 314.0). However, the use of IC-CD is limited to the determination of trace analytes in the presence of high concentrations of other anions. For instance, a recent study (*17*) has shown *p*-chlorobenzene sulfonate co-eluted with perchlorate using the standard IC-CD method (EPA Method 314.0). Mass spectrometry has also been applied for the detection of perchlorate in different matrices, commonly coupled with an ion chromatograph (IC-MS) (*5*, *18*−*21*) or ion exchange chromatograph (IEC-MS) (*1*, *2*, *22*). Reverse phase high-performance liquid chromatography with tandem mass spectrometry (RP-HPLC−MS/MS) (*23*) was used for the determination of the amount of perchlorate in water using a Synergi Max-RP C_{12} column (250 mm × 4.6 mm, 4 μm) with a long analysis time of 8.1 min. Unfortunately, the long analysis time does not meet the requirement of high-throughput sample analysis. Perchlorate was first detected in human breast milk by Kirk et al. in 2005 using IC-MS (*21*) and has subsequently been reported in several publications (*20*, *24*). The method reporting limit (MRL) was 0.4 μg/L (*21*). No study of the determination of perchlorate in milk powder using hydrophilic interaction chromatography combined with tandem mass spectrometry (HILIC−MS/MS) has yet been reported.

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Table 1. Mass Spectral Parameters

ion source voltage (V)	−4500
ion source temperature (°C)	700
curtain gas (psi)	35
nebulizer gas (psi)	70
auxiliary gas (psi)	70
DP	−45
CE	−34

The objective of this study is to develop a fast and sensitive HILIC−MS/MS method for analyzing perchlorate in milk powder and milk after solid phase extraction with MDLs of 4.00×10^{-3} μg/g and 8×10^{-2} μg/L, respectively, and a short analysis time of 3.5 min.

MATERIALS AND METHODS

Materials. A 1000 mg/L standard solution of perchlorate was obtained from GFS Chemicals (Powell, OH). Acetonitrile, methanol, and formic acid (HPLC grade) were purchased from Dikma (Richmond Hill, NY). Sample solutions were prepared in 18.3 MΩ cm Millipore water (Milli-Q, Millipore) and filtered through a 0.22 μm filter (PTFE).

Dilutions of the stock standard (1000 mg/L) were used to construct a seven-point calibration curve. All the calibration standards were stored at room temperature.

High-Performance Liquid Chromatography and Mass Spectrometry. Chromatography was performed on an Agilent 1200 system with an autosampler, and the temperature of the analytical column was controlled with a column oven. An Inertsil HILIC column (150 mm × 3.0 mm, 3.5 μm) was employed for analyte separation. The column temperature was maintained at room temperature. The mobile phase was a mixture of methanol and 0.1% formic acid (60:40, v/v), and the flow rate was kept constant at 0.35 mL/min. The injection volume was 5 μL.

Detection was performed on a Sciex API 4000 Q Trap MS system equipped with a Turbo Ionspray interface. Mass spectral parameters were optimized, and the results are listed in **Table 1**. Quantification was performed using multiple-reaction monitoring (MRM) of the m/z 98.8 → m/z 82.9 (Cl^{35}) and m/z 100.8 → m/z 84.9 (Cl^{37}) transitions for perchlorate. Data acquisition and processing were performed with Analyst version 4.1.2.

Sample Preparation. For the milk experiments, 5 mL of 1% acetic acid and 20 mL of acetonitrile were added to 5 mL of milk, and the mixture was vortexed for 60 s. After being centrifuged at 3500*g* for 5 min, the supernatant was decanted and loaded in a Strata X SPE cartridge, which was preconditioned with 3 mL aliquots of acetonitrile and 3 mL aliquots of water. The milk solution was passed through the cartridge at a flow rate of 2 mL/min, and the eluent was collected in a 50 mL tube. After the supernatant solution had passed completely through the cartridge, the cartridge was rinsed with 6 mL of Millipore water. The wash was also collected in the 50 mL tube. Millipore water was added to the tube to give a final volume of 40 mL. The solution was then filtered through a 0.22 μm filter, and 5 μL was injected into the HILIC−MS/MS system.

For the milk powder experiments, milk powder (~1 g) was dissolved in 50 mL of Millipore water. A subsample of 5 mL of the solution was removed and prepared via the previously described preparation method for milk.

RESULTS AND DISCUSSION

Optimization of the HPLC−MS/MS Method. Several columns were used for the determination of the amount of perchlorate: ZorBax Eclipse XDB-C_{18} column (150 mm × 2.1 mm, 3.5 μm), ZorBax Eclipse XDB-C_8 column (150 mm × 2.1 mm, 3.5 μm), Synergi Max-RP column (250 mm × 4.6 mm, 4 μm), and Inertsil HILIC column (150 mm × 3.0 mm, 3.5 μm). Perchlorate had no retention on the C_{18} and C_8 columns. The retention times of perchlorate on the Synergi Max-RP and HILIC columns were 8.1 and 2.25 min, respectively (**Figure 1**). The Synergi Max-RP column is a C_{12} material and has a bonding density 25% higher than those of typical C_{18} columns. After the optimization of the composition of the mobile phase and the flow rate, the retention time of perchlorate on the C_{12} column was still very long. The response of perchlorate on the two columns was similar. The Inertsil HILIC column (150 mm × 3.0 mm, 5 μm) was chosen to shorten the run time. The retention time was much shorter than that reported in the literature, such as 10.56 (*26*), 9.23 (*27*), and ~6 min(*28*). The short analysis time better meets the requirements for high sample throughput in our study.

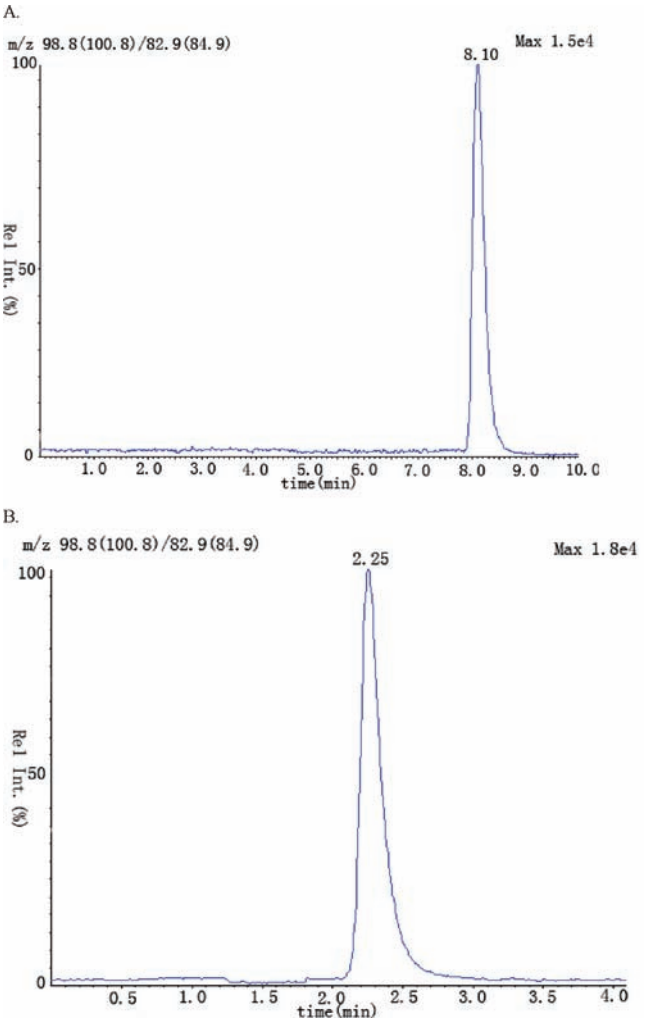

Figure 1. Chromatography of perchlorate using (**A**) a Synergi Max-RP column (250 mm × 4.6 mm, 4 μm) and (**B**) an Inertsil HILIC column (150 mm × 3.0 mm, 3.5 μm).

The highly polar contents could not be retained on the C_{18} or C_8 column; thus, all components were simultaneously eluted in the dead time. As shown in **Figure 1**, the polar compounds were well separated when HILIC was applied, which means HILIC will be an effective technique for analyzing the highly polar compounds. The retention mechanism for HILIC was a partitioning between the bulk eluents and a water-rich layer, partially immobilized on the stationary phase (*25*). An acetonitrile/methanol/water mixture could be used as the mobile phase for HILIC and produce effective ionization. On the other hand, the requirement of salt in the mobile phase for IC and IEC reduced efficient ionization when coupled with MS detection. The use of an aqueous solution as the eluting solvent provided a number of advantages to HILIC over the conventional normal phase chromatography (NPC) where the nonpolar solvents (often based on hexane) were used as the mobile phase. The difference in polarity generally limited the solubility of the polar compounds in the eluents in NPC. The use of an organic solvent also restricted

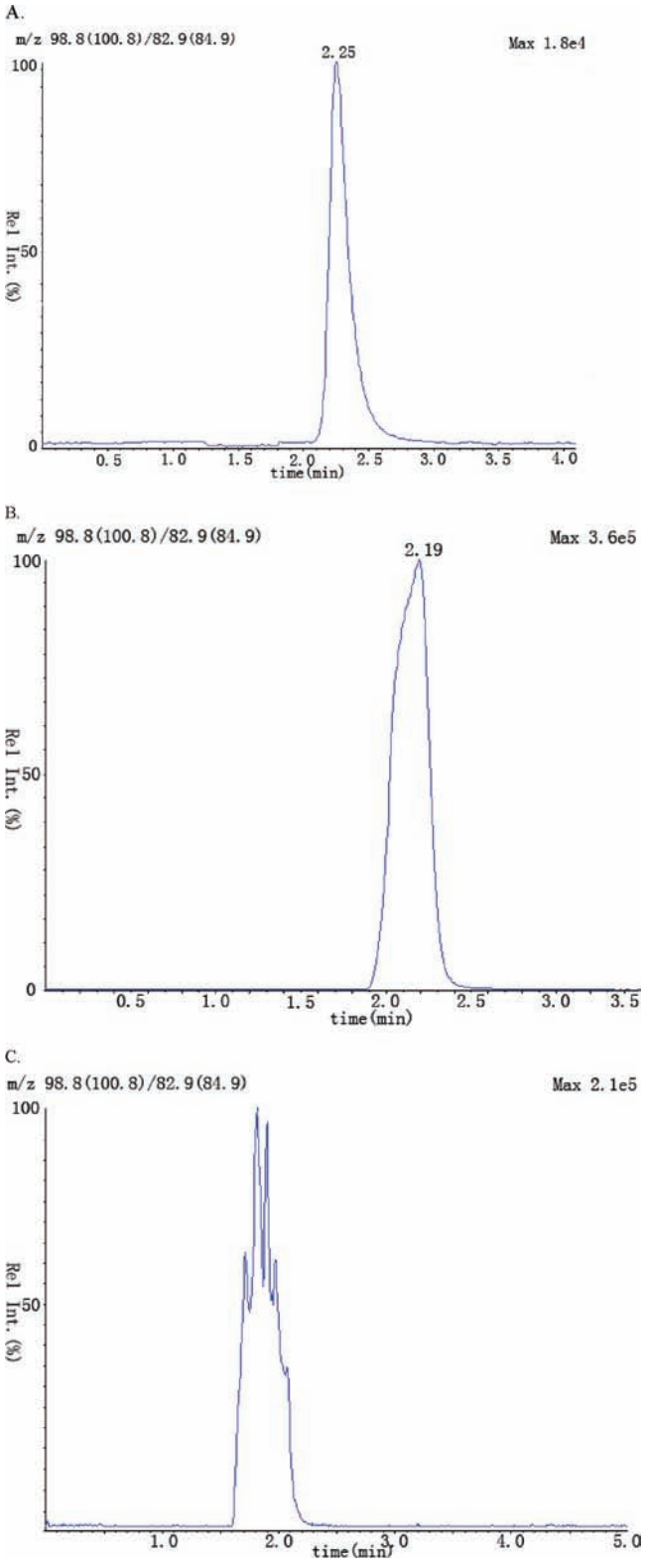

Figure 2. Chromatography of perchlorate (10 ng/mL) using different mobile phases: (**A**) methanol with 0.1% formic acid, (**B**) acetonitrile with 0.1% formic acid, and (**C**) methanol with 10 mM NH_4AC.

the usage of electrospray MS since ionization is not easily achieved in totally organic, nonpolar eluents. In addition, the elution order in HILIC is the opposite of that seen in RP separations (*25*). This means that HILIC may be the best choice for the analytes, which encountered a problem with RPLC analysis.

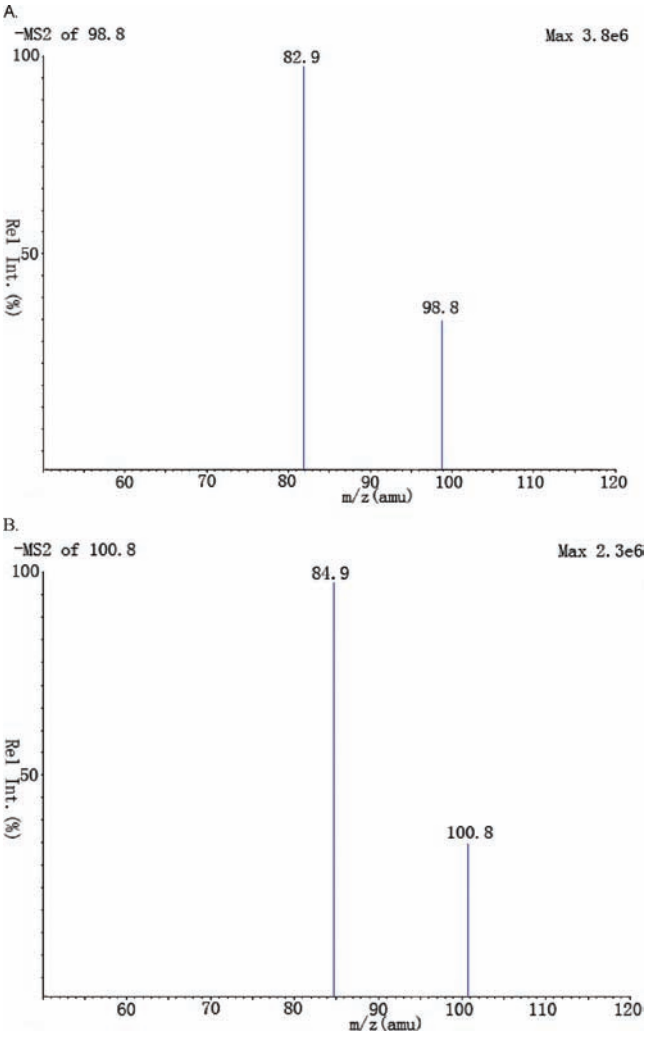

Figure 3. Product ion spectrum of perchlorate.

The separation and ionization of the analytes were affected by the composition of the mobile phase. An attempt was made to add formic acid and ammonium acetate to the mobile phase. The peak shape of perchlorate was very poor when using water with ammonium acetate as the aqueous phase (**Figure 2**). Methanol and acetonitrile were also tested to give a stronger response and better peak shape of perchlorate. Though acetonitrile can give a slightly stronger response than methanol, the peak shape was still not satisfactory (**Figure 2**). The effect of 0.1, 0.2, and 0.5% formic acid in the aqueous phase on the response of perchlorate was investigated; the response showed practically no difference. A mixture of water with 0.1% formic acid and methanol was finally adopted as the mobile phase. It is much more compatible with mass spectrometry than the mobile phase used in the literature for IC-MS (*18*−*21*, *28*) or IEC-MS (*1*, *2*, *22*).

Electrospray ionization (ESI) is the most common method of sample introduction. As a soft ionization technique, ESI results in less analyte fragmentation and, subsequently, less complicated spectral data. The MS/MS operation parameters were carefully optimized for determination of the amount of perchlorate. The mass spectrometer was tuned in both positive and negative ionization modes with ESI for perchlorate. The signal intensity obtained in negative ionization mode was $\sim 1.7 \times 10^7$. This result was much higher than that in positive mode, which was $\sim 1.0 \times 10^3$. In the precursor ion full scan spectra, the most abundant ions were $[M - H]^-$ at m/z 98.8 (Cl^{35}) and m/z 100.8 (Cl^{37}) for perchlorate, and the signals can be reproduced. The product ion

Table 2. Results[a] of the Recovery and Precision Test ($n = 6$)

	spiking level		concentration		mean recovery (%)		RSD (%) intraday		RSD (%) interday	
compound	A (μg/g)	B (μg/L)	A (μg/g)	B (μg/L)	A	B	A	B	A	B
perchlorate	0.0200	0.400	0.0370	0.373	92.5	93.2	5.8	12	6.7	5.7
	4.00	5.00	3.80	4.78	95.6	94.5	8.2	7.3	5.2	4.8
	8.00	20.0	7.30	18.3	91.3	96.8	3.4	1.2	9.3	6.9

[a] A stands for milk powder and B for milk.

scan spectra showed a high abundance of fragment ions at m/z 82.9 and 84.9 for perchlorate. Multiple-reaction monitoring (MRM) using the precursor → product ion transitions (m/z 98.8 → m/z 82.9 and m/z 100.8 → m/z 84.9) was employed for quantification of perchlorate, so that confirmation and quantification of perchlorate are based not only on the uniformity of retention times but also on the 3:1 natural isotopic ratio of ^{35}Cl to ^{37}Cl. The product ion spectrum of perchlorate is shown in **Figure 3**.

Sample Preparation. Solid phase extraction (SPE) was employed for sample cleanup and pretreatment of the samples prior to HPLC−MS/MS analysis. SPE is simpler and faster than liquid−liquid extraction and uses less organic solvent. A Strata-X SPE cartridge, a modified styrene-divinylbenzene polymer suitable for a wide range of basic, neutral, and acidic compounds, was used in this study. It had high extraction efficiency regardless of the sample pH. In this study, perchlorate was a highly polar compound. Most of the compound simply passed through the SPE cartridge; however, the interference from the matrix was retained on the cartridge. Water was used to again wash the cartridge, in case it retained a small volume of perchlorate. The recovery of the method for perchlorate was greater than 90%.

Calibration Curve. *Milk*. The calibration curve was linear within the concentration range of 4.00×10^{-1} to 20.0 μg/L, and the calibration equation for perchlorate was $y = 4.85 \times 10^4 x + 776$ with $r = 0.9938$.

Milk Powder. The calibration curve was linear within the concentration range of 2.00×10^{-2} to 8.00 μg/g, and the calibration equation for perchlorate was $y = 7.83 \times 10^{-4} x + 22.58 \times 10^{-4}$ with $r = 0.9982$.

The MDLs for perchlorate in milk powder and milk were 4.00×10^{-3} μg/g and 8.00×10^{-2} μg/L, respectively, with an injection volume of 5 μL. The MDL was much lower than those reported in the literature (*26*, *27*), which were higher than 3 μg/L in milk with an injection volume of 1 mL.

Precision and Accuracy. The precision and accuracy of the analysis are reported as recoveries and relative standard deviations or relative percentage differences.

Milk Powder. To evaluate the precision and accuracy of the method, milk powder samples spiked with perchlorate at three concentrations (2.00×10^{-2}, 4.00, and 8.00 μg/g) were analyzed, and each sample was assessed in six replicates for three consecutive days.

Milk. Milk samples spiked with perchlorate at three concentrations (4.00×10^{-1}, 5.00, and 20.0 μg/L) were analyzed, and each sample was assessed in six replicates for three consecutive days.

The results are presented in **Table 2**. Precision (%RSD) values ranged from 1.2 to 12%, indicating good reproducibility of the method. Calculated concentrations were compared to theoretical concentrations to determine the recovery. They were generally between 91.3 and 96.8%, indicating that the method was sufficiently accurate for the analysis of the perchlorate in milk powder and milk.

Table 3. Results for Milk Powder Samples

	result (μg/g)			result (μg/g)	
sample	HPLC−MS/MS	HILIC−MS/MS	sample	HPLC−MS/MS	HILIC−MS/MS
1	0.895	0.911	7	0.533	0.524
2	0.692	0.675	8	0.654	0.609
3	not detected	not detected	9	0.305	0.325
4	0.868	0.886	10	0.812	0.785
5	0.689	0.652	11	not detected	not detected
6	0.656	0.646	12	0.455	0.423

Table 4. Results for Milk Samples

	result (μg/L)			result (μg/L)	
sample	HPLC−MS/MS	HILIC−MS/MS	sample	HPLC−MS/MS	HILIC−MS/MS
1	2.79	2.82	6	3.68	3.64
2	2.85	2.85	7	1.32	1.34
3	3.28	3.26	8	3.00	3.00
4	3.32	3.38	9	2.38	2.38
5	2.11	2.03	10	4.10	4.10

Matrix Effect. *Milk Powder*. To eliminate the matrix effect, calibration standards were prepared in a matrix. The matrix effect was measured by comparing the response of sample spiked postextraction (A) with that of the standard solution containing equivalent amounts of perchlorate (B). The ratio [$(A/B \times 100)$%] was used to evaluate the matrix effect. Three concentrations (2.00×10^{-2}, 4.00, and 8.00 μg/g) were investigated. The mean result was 98.5%.

Milk. Calibration standards could not be prepared in a matrix because of the lack of a blank matrix. Millipore water was used to prepare the calibration standards. The matrix effect was evaluated by comparing the calculated quality of sample spiked postextraction (A) with the theoretical added quality of perchlorate (B). The mean result was 95.6%.

The results for milk powder and milk indicated that the matrix effect did not influence the determination of the amount of perchlorate. There are also some reports (*26*−*29*) using isotopically labeled perchlorate as an internal standard to compensate for the matrix effect.

Method Applied to the Analysis of Milk Powder and Milk Samples. The newly developed method has been successfully applied to determine the amount of perchlorate in milk powder and milk.

Milk Powder. Twelve milk powder samples from different sources were analyzed. The results are listed in **Table 3**. Except for two samples, all the others contained measurable levels of perchlorate. The mean perchlorate content in milk powder was 0.640 μg/g, with the highest value being 0.911 μg/g.

Milk Samples. Ten milk samples from different sources were analyzed. The results are listed in **Table 4**. All the samples contained measurable levels of perchlorate. The mean perchlorate content in milk samples was 2.88 μg/L, with the highest value being 4.10 μg/L.

The same samples were analyzed in another laboratory (State Key Laboratory of Organic Geochemistry, Guangzhou Institute of Geochemistry, Chinese Academy of Science) by HPLC−MS/MS. Each laboratory was blind to the result obtained by the other laboratory. The agreement between the two independent methods and laboratories was very good (**Table 3**), and the unambiguous mass spectrometric identification left little doubt that perchlorate anion was present in these milk powder and milk samples.

A sensitive, rapid, and specific HILIC−MS/MS method for the determination of the amount of perchlorate in milk powder and milk was developed. The use of a hydrophilic column enabled the separation of perchlorate in a short time without the need for ion pair reagents. The samples were cleaned using a Strata-X SPE cartridge prior to the HILIC analysis. The method has been used to quantify perchlorate in milk powder and milk.

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