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ORIGINAL ARTICLE

Chlorine isotopic composition of perchlorate in human urine as a means of distinguishing among exposure sources

Armen Poghosyan[1], Maria Morel-Espinosa[2], Liza Valentin-Blasini[2], Benjamin C. Blount[2], Catterina Ferreccio[3], Craig M. Steinmaus[4] and Neil C. Sturchio[1,5]

Perchlorate (ClO_4^-) is a ubiquitous environmental contaminant with high human exposure potential. Natural perchlorate forms in the atmosphere from where it deposits onto the surface of Earth, whereas synthetic perchlorate is manufactured as an oxidant for industrial, aerospace, and military applications. Perchlorate exposure can potentially cause adverse health effects in humans by interfering with the production of thyroid hormones through competitively blocking iodide uptake. To control and reduce perchlorate exposure, the contributions of different sources of perchlorate exposure need to be quantified. Thus, we demonstrate a novel approach for determining the contribution of different perchlorate exposure sources by quantifying stable and radioactive chlorine isotopes of perchlorate extracted from composite urine samples from two distinct populations: one in Atlanta, USA and one in Taltal, Chile (Atacama region). Urinary perchlorate from the Atlanta region resembles indigenous natural perchlorate from the western USA ($\delta^{37}Cl = +4.1 \pm 1.0‰$; $^{36}Cl/Cl = 1\,811\ (\pm 136) \times 10^{-15}$), and urinary perchlorate from the Taltal, Chile region is similar to natural perchlorate in nitrate salt deposits from the Atacama Desert of northern Chile ($\delta^{37}Cl = -11.0 \pm 1.0‰$; $^{36}Cl/Cl = 254\ (\pm 40) \times 10^{-15}$). Neither urinary perchlorate resembled the isotopic pattern found in synthetic perchlorate. These results indicate that natural perchlorate of regional provenance is the dominant exposure source for the two sample populations, and that chlorine isotope ratios provide a robust tool for elucidating perchlorate exposure pathways.

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INTRODUCTION

Perchlorate (ClO_4^-) is a highly oxidized anion and is a widespread contaminant that when ingested can potentially cause adverse health effects in humans. Once in the body, perchlorate can competitively block iodide from entering the thyroid, potentially affecting further production of thyroid hormones. Deficiency of thyroid hormones has severe health effects especially for fetuses, infants, and young children. Because the thyroid hormones are crucial for neurodevelopment in the early stages of life, their deficiency can cause irreversible impairment in the nervous system, particularly in the brain.[1–5]

Perchlorate has been detected in surface water and groundwater across the United States[6–15] as well as in a wide range of food products including milk, infant formulas, fruits, and vegetables.[16–22] The primary routes of perchlorate exposure to humans appear to be through oral intake of food and drinking water.[22–26] Perchlorate has been detected in human US breast milk[17,27–29] and in all urine samples tested as part of the National Health and Nutrition Examination Surveys between 2001 and 2008,[30,31] indicating widespread human exposure across the United States. Urinary perchlorate is an indicator of exposure since perchlorate is not metabolized and exits the body primarily through urine.[32] Children are exposed to significantly higher doses of perchlorate compared with adults, likely because of higher rates of consumption of foods that tend to contain higher perchlorate levels.[22,33,34]

Perchlorate originates from different natural and manufactured sources that can be distinguished by their relative isotopic signatures based on the stable chlorine isotope ratios reported in the conventional delta (δ) notation and on $^{36}Cl/Cl$ ratios. Perchlorate that forms in the atmosphere deposits onto the surface of Earth, but it accumulates mainly in dry regions such as the Atacama Desert in Chile and the Death Valley in the United States.[35–41] Two main types of isotopically distinct natural perchlorate have been reported to date: one type having generally heavier $\delta^{37}Cl$ values (–4‰ to +6‰) combined with relatively high $^{36}Cl/Cl$ ratios (3100×10^{-15} to $66{,}500 \times 10^{-15}$) has been found at locations across the United States; and the second type characterized by anomalously low $\delta^{37}Cl$ values (–14.3‰ to – 11.8‰) and relatively low $^{36}Cl/Cl$ ratios (22×10^{-15} to 590×10^{-15}) has been found only in the Atacama Desert of northern Chile.[10,15,42,43] Atacama perchlorate is associated with nitrate-rich caliche deposits and is by far the largest known reservoir of natural perchlorate on Earth.[8,35,44,45] Substantial quantities of Atacama perchlorate were introduced into the environment across the United States during the first half of the 20th century due to the

[1]Department of Earth and Environmental Sciences, University of Illinois at Chicago, Chicago, Illinois, USA; [2]Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia, USA; [3]CENTRO FONDAP/ACCDIS, Pontificia Universidad Católica de Chile, Santiago, Chile and [4]Arsenic Health Effects Research Program, School of Public Health, University of California, Berkeley, California, USA. Correspondence: Dr. Armen Poghosyan, Department of Earth and Environmental Sciences, University of Illinois at Chicago, 845 West Taylor Street, MC-186, Chicago, IL 60607-7059, USA.
Tel.: +1 267 207 1366.
E-mail: apogho2@uic.edu and armenpogh@hotmail.com
[5]Present address: Department of Geological Sciences, University of Delaware, Newark, Delaware 19716, USA
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widespread application of imported Chilean nitrate fertilizer.[36,46–48] Synthetic perchlorate is primarily used as an oxidant in a variety of solid rocket propellants and explosives as well as in consumer products including fireworks, matches, air bags, chlorine bleach, safety flares, and chlorate herbicides.[9,49–51] The isotopic composition of synthetic perchlorate is distinctly different from both types of natural perchlorate in its relatively consistent δ^{37}Cl value ($+0.6 \pm 1.0$‰) and its low ^{36}Cl/Cl ratio (1×10^{-15} to 40×10^{-15}).[10,43,52]

Recent studies evaluated dietary sources of perchlorate in the United States by estimating overall perchlorate contribution to the food chain from all potential sources[46] or by using quantities of perchlorate in different food products, drinking water, and urine.[22,23] However, none of these studies can differentiate between indigenous natural perchlorate, natural Atacama perchlorate, and synthetic perchlorate as the primary source of perchlorate exposure. The objective of this study was to identify the exposure source of perchlorate by measuring the chlorine isotopic composition (δ^{37}Cl, ^{36}Cl/Cl) of perchlorate extracted from urine. This novel approach can distinguish between all potential sources of perchlorate, and identify the primary source of perchlorate exposure. We hypothesized that the chlorine isotopic composition of urinary perchlorate would resemble that of groundwater, surface water, and soil in the geographical region of the population.

METHODS

Sample Collection

Perchlorate was extracted from composite urine samples for isotopic analysis by using 100 cm^3 clear PVC columns filled with Purolite A530E bifunctional anion exchange resin. This resin is exceptionally selective for perchlorate,[53–55] and similar columns have previously been used to extract perchlorate from surface water and groundwater.[11–13,15,42,56] Detailed description of sampling column design and isotopic analytical procedures are given by Hatzinger et al.[57] The first perchlorate sample was extracted from a total volume of 40-l urine pooled from ~133 anonymously collected urines from residents of the Atlanta metro area over a 2-week collection period. The second sample was extracted from a total volume of 1.05-l urine pooled from 49 clinical residual urine samples collected from adult residents of Taltal, Chile (Atacama region). Human specimen use was in accordance with human subjects review (University of California, Berkeley). After sampling was completed, the resin columns were shipped to the University of Illinois at Chicago in a cooler filled with ice packs, and the sample columns were kept refrigerated until analysis. The amounts of perchlorate retained on each column was estimated by analyzing perchlorate concentrations in urine samples before and after the Purolite columns by using an ion chromatography tandem mass spectrometry (IC-MS/MS) at CDC.[58] Aliquots were run in triplicates for each composite sample.

Extraction of perchlorate from the resin columns was performed using procedures described by Hatzinger et al.[57] Briefly, the resin was ultrasonically cleaned in deionized water, and then it was flushed with 4-M HCl to remove common anions including organic acids. Subsequently, perchlorate was eluted with 1-M $FeCl_3$–4-M HCl,[55] and iron was removed by passing the diluted eluant through a cation-exchange resin, then the iron-free solution was evaporated to ~2 ml volume. The final purification of perchlorate was performed by chromatography, then perchlorate was precipitated and recrystallized as tetra-*n*-pentylammonium perchlorate ($TPAClO_4$).[59] The overall sample processing blank for perchlorate was 5 μg, which was $< 5\%$ of the perchlorate recovered for isotopic analysis.[60]

Stable Cl Isotope Analysis (δ^{37}Cl) of Perchlorate by SIMS

The stable chlorine isotope ratio (^{37}Cl/^{35}Cl) in perchlorate is normally analyzed by isotope ratio mass spectrometry (IRMS).[10,11,42] However, we used secondary ion mass spectrometry (SIMS) for stable chlorine isotope ratio measurements because of the small sample size. All analyses were performed on $TPAClO_4$. Samples were mounted by pressing into indium metal in a 2.5-cm diameter sample holder and coating the surface with 50 nm of vapor-deposited gold. SIMS analyses were performed at the Center for Microanalysis of California Institute of Technology on an IMS 7 f-GEO (CAMECA, Gennevilliers, France). Analyses were performed with a 10-keV Cs^+ primary ion beam. The ion beam was focused to a diameter of ~20 μm with 5–6 nA of beam current. All isotope ratio analyses were performed by pre-sputtering of a 100×100 μm raster area for 120 s, and then scanning a 75×75 μm raster during data collection. ^{34}SH contribution to ^{35}Cl results was negligible at a mass-resolving power (M/ΔM) of 1200 defined at the full width at 10% of the maximum peak height; this was also confirmed under a resolution of 5000. An energy bandwidth of 45 eV was set for all SIMS measurements, and secondary ion accelerating voltage was −9 keV for all isotopic analyses. Chlorine isotopes ^{35}Cl and ^{37}Cl were measured by Faraday cups with data collection times of 1 and 2 s per cycle, respectively, for a total of 20 cycles. Data are normalized to measurements of $KClO_4$ isotopic reference materials USGS37 and USGS38,[11] which were converted to $TPAClO_4$ prior to measurement. Stable chlorine isotope ratios are reported in the conventional delta (δ) notation, as follows:

$$\delta^{37}\mathrm{Cl}(‰) = \left[\left({}^{37}\mathrm{Cl}/{}^{35}\mathrm{Cl} \right)_{\mathrm{sample}} / \left({}^{37}\mathrm{Cl}/{}^{35}\mathrm{Cl} \right)_{\mathrm{SMOC}} - 1 \right] \times 1000$$

Where SMOC is the isotopic reference standard mean ocean chloride.[61] Analytical precision corresponding to 1σ for δ^{37}Cl values determined from replicate measurements of reference materials is ±1.0‰.

^{36}Cl Abundance Analysis by Accelerator Mass Spectrometry

After the analysis of the stable chlorine isotope ratios by SIMS, the remaining samples were scraped from the indium metal sample holders and diluted with USGS37 standard in $TPAClO_4$ form and homogenized by dissolving in 2-ml acetone. Sample J-1183 (Atlanta, USA) was diluted ~3.8 times, whereas sample J-1184 (Taltal, Chile) was diluted ~3.1 times, in order to get a larger sample size to facilitate loading of AgCl targets for accelerator mass spectrometry (AMS) measurements. Then, the diluted perchlorate samples were converted from $TPAClO_4$ to $KClO_4$ by using 0.5-mol/l KOH in absolute ethanol solution, and the $KClO_4$ was sealed under vacuum into 20-cm lengths of 9-mm outer diameter borosilicate glass tubing. Afterwards, $KClO_4$ was heated for 30 min at 600 °C in order to decompose $KClO_4$ according to the following reaction: $KClO_4 \rightarrow KCl + 2\ O_2$ (g). Subsequently, the chloride from KCl was purified by a standard ion chromatography method developed by the Purdue Rare Isotope Measurement (PRIME) Laboratory for ^{36}Cl analyses, and then the chloride was precipitated as AgCl, which was used as a target material for the measurements of radioactive ^{36}Cl isotopic abundances by AMS. Samples for the ^{36}Cl abundances were analyzed at the PRIME Laboratory at Purdue University. The ^{36}Cl results were corrected for the instrumental background and are reported in units of ^{36}Cl/Cl $\times 10^{-15}$ along with errors based on counting statistics.

Comparative Isotopic Patterns

Chlorine-36 has previously been shown to be an effective tracer of the origin of perchlorate in various environmental matrices.[15,43] Previous work indicates unique clustering of ^{36}Cl/Cl ratios *vs* δ^{37}Cl values for perchlorate extracted from synthetic perchlorate, natural perchlorate from Atacama (Chile), and natural perchlorate from the western USA.[42,43] The chlorine isotope pattern for synthetic perchlorate was defined based on analysis of laboratory grade perchlorate salts. The chlorine isotope pattern for natural perchlorate indigenous of the western USA was extracted from groundwater and soil samples collected from Texas, New Mexico, California, and Oregon. The chlorine isotope pattern for natural perchlorate from the Atacama Desert was characterized based on bulk soil and groundwater samples collected in that region.[42,43] Concentration ellipses were computed using the "dataEllipse" function in the CAR (Companion to Applied Regression)[62] package of R, an open source software environment for statistical computing and graphics,[63] based on a bivariate normal distribution fit to the ^{36}Cl/Cl ratios and δ^{37}Cl values of perchlorate reference materials. The concentration ellipses define the confidence curves within which 95% of the data is expected to lie, assuming a bivariate normality.

RESULTS

Two perchlorate samples were extracted from composite urine samples collected from geographically distinct populations located in Atlanta, USA and Taltal, Chile regions for chlorine isotopic analyses of perchlorate. A total of ~202 μg of urinary

Table 1. Stable and radioactive chlorine isotope ratios of perchlorate extracted from urine from Atlanta, USA and Taltal, Chile regions.

Sample ID	*Sample location*	*Urine sample volume (l)*	*ClO_4^- on the column (μg)*	*Final ClO_4^- recovered (μg)*	*$\delta^{37}Cl_{SMOC}$ (‰)*	*$^{36}Cl/Cl$ (10^{-15})*
J-1183	Atlanta, USA	40	198	202	$+4.1 \pm 1$	1811 ± 136
J-1184	Taltal, Chile	1.05	154	155	-11.0 ± 1	254 ± 40

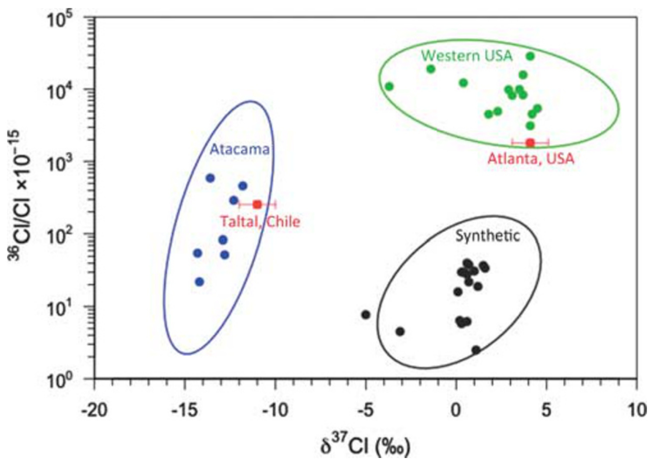

Figure 1. Diagram comparing $^{36}Cl/Cl$ ratios *vs* $\delta^{37}Cl$ values for perchlorate extracted from urine from residents of the Atlanta, USA metro area and Taltal, Chile (Atacama region), in comparison with synthetic perchlorate, and natural perchlorate from Atacama (Chile) and the western USA.[42,43,64] $^{36}Cl/Cl$ errors are smaller than data points. The concentration ellipses define the confidence curves within which 95% of the data is expected to lie, assuming bivariate normality.

perchlorate was recovered from the composite urine sample collected from the sample population of the Atlanta metro area, and ~155 μg of urinary perchlorate was recovered from the composite urine sample collected from the residents of Taltal, Chile (Table 1). The amounts of perchlorate retained on each column and the final yields of purified perchlorate were independently determined, and the estimates agreed well for both perchlorate samples.

The urinary perchlorate samples were analyzed for the stable ($\delta^{37}Cl$) and radioactive ($^{36}Cl/Cl$) chlorine isotopic signatures in order to identify the primary exposure sources of perchlorate. The results demonstrate that the urinary perchlorate sample from the Atlanta area had a positive $\delta^{37}Cl$ value of $+4.1 \pm 1.0$‰ and a relatively high $^{36}Cl/Cl$ ratio of 1 811 (±136) $\times 10^{-15}$ (Table 1). In contrast, the perchlorate sample extracted from the composite urine sample collected from multiple residents of Taltal, Chile had significantly lower stable chlorine isotopic signature ($\delta^{37}Cl$ value) of -11.0 ± 1.0‰ and lower radioactive chlorine isotopic abundance ($^{36}Cl/Cl$ ratio) of 254 (±40) $\times 10^{-15}$ compared to the urinary perchlorate from the Atlanta region.

DISCUSSION

The chlorine isotopic compositions of perchlorate samples collected from the three known principal environmental sources of perchlorate in the United States and composite urine samples from Atlanta, USA and Taltal, Chile define three distinct, non-overlapping clusters in a diagram of $^{36}Cl/Cl$ as a function of $\delta^{37}Cl$ (Figure 1). The isotopic composition of indigenous natural perchlorate from the western USA appears to be rather consistent over a wide portion of North America in terms of $\delta^{37}Cl$ values and $^{36}Cl/Cl$ ratios. Similar isotopic signatures were observed in perchlorate from Texas, New Mexico, California, Oregon, and throughout the Great Lakes.[15,42,43,64] Indigenous natural perchlorate samples collected from the western USA and from the Great Lakes have the highest $^{36}Cl/Cl$ ratios (3100×10^{-15} to $66{,}500 \times 10^{-15}$) yet reported for perchlorate, and a range of $\delta^{37}Cl$ values from −4‰ to +6‰. The Atacama Desert samples have much lower $^{36}Cl/Cl$ ratios (ranging from 22×10^{-15} to 590×10^{-15}) and $\delta^{37}Cl$ values (−14.3‰ to −11.8‰) compared with those of indigenous natural perchlorate from the US. Synthetic perchlorate samples have $\delta^{37}Cl$ values in the range 0.2‰ to 1.6‰ and $^{36}Cl/Cl$ ratios of 1×10^{-15} to 40×10^{-15}, which is consistent with a predominantly marine source of Cl in the brine used as for electrolytic production of perchlorate.[43,65]

The urinary perchlorate sample from the Atlanta region more closely aligns with indigenous natural perchlorate extracted from groundwater and soil samples from the United States[42,43] in terms of its $\delta^{37}Cl$ value and $^{36}Cl/Cl$ ratio, indicating indigenous natural perchlorate as the primary source of exposure in the sampled Atlanta residents (Figure 1). Any addition of synthetic or Atacama perchlorate would reduce the ^{36}Cl abundance in the urinary perchlorate sample from the Atlanta region, while also shifting the $\delta^{37}Cl$ result toward lower values on Figure 1 since both synthetic and Atacama perchlorates have lower $\delta^{37}Cl$ values than indigenous natural perchlorate from the United States. Overall, the shift in the $\delta^{37}Cl$ value appears to be minimal in the Atlanta sample, but the ^{36}Cl abundance is somewhat lower, compared with indigenous United States perchlorate. These features indicate negligible Atacama perchlorate contribution since it would produce a much larger shift in the $\delta^{37}Cl$ value. However, a minor synthetic perchlorate contribution to a dominantly indigenous natural source could possibly explain both the $\delta^{37}Cl$ value and the $^{36}Cl/Cl$ ratio of the Atlanta urinary perchlorate sample.

The $\delta^{37}Cl$ value and $^{36}Cl/Cl$ ratio determined for perchlorate from the urine of residents from Taltal, Chile (Atacama region) are similar to perchlorate samples collected from the Atacama region, indicating that natural Atacama perchlorate is the main source of exposure in that region (Figure 1). Perchlorate contributions from synthetic or young atmospherically produced perchlorate appear to be relatively minor, because any synthetic perchlorate contribution would increase the $\delta^{37}Cl$ value and decrease the ^{36}Cl abundance, whereas addition of significant quantities of young atmospheric perchlorate would increase the ^{36}Cl abundance while preserving the $\delta^{37}Cl$ value if we assume that the chlorine sources for atmospheric perchlorate formation in a given region have relatively constant $\delta^{37}Cl$ value over time.

Indigenous natural perchlorate samples having anomalously high $^{36}Cl/Cl$ ratios may have been affected by the presence of the bomb-produced ^{36}Cl pulse from the 1952–1962 thermonuclear tests.[15,43] However, $^{36}Cl/Cl$ ratios $> 8000 \times 10^{-15}$ were also measured in perchlorate extracted from southwest US groundwater having ^{14}C ages of > 10 ka.[43] Even the lowest $^{36}Cl/Cl$ ratio of $\sim 3100 \times 10^{-15}$ in indigenous perchlorate from pre-bomb groundwater is much higher than the highest pre-bomb $^{36}Cl/Cl$ ratio of $\sim 1200 \times 10^{-15}$ in meteoric chloride near the Earth's surface across the US.[66,67] The stratosphere is the only known location that has sufficiently high ^{36}Cl isotopic abundances[68] to account for the observed $^{36}Cl/Cl$ ratios in indigenous perchlorate samples from the western US as well as in the urinary perchlorate sample from the Atlanta region, which strongly indicates that indigenous natural perchlorate is the dominant source of urinary perchlorate from Atlanta, USA.

The $^{36}Cl/Cl$ ratios in natural Atacama perchlorate samples are significantly lower compared to those in the indigenous natural perchlorate from the western US, which might be explained chronologically since Atacama perchlorate is much older than the western US perchlorate.[69,70] The low $^{36}Cl/Cl$ ratios in synthetic perchlorate are consistent with chloride sources from ancient marine halite deposits.[43] Thus, the ^{36}Cl signature along with the stable chlorine isotope of perchlorate is a valuable tool, which can be used for tracing the source and origin of perchlorates in the environment. Although not analyzed in this study, stable oxygen isotopes ($\delta^{18}O$, $\Delta^{17}O$) of perchlorate offer additional tools for identifying perchlorate sources and origin.[10–13,15,42,56,71]

In summary, our results demonstrate the use of chlorine isotope ratios of perchlorate extracted from pooled human urine samples for identifying the primary sources of perchlorate exposure in two geographically distinct sample populations. This novel method appears to be a robust approach, which can be used for differentiating between indigenous natural perchlorate, Atacama perchlorate and synthetic perchlorate as the primary source of perchlorate exposure, because the perchlorate molecule is stable in the environment, as well as *in vivo*,[32] and can apparently retain its initial isotopic composition for centuries to millennia in groundwater and surface water systems.[57,72] The isotopic identification of perchlorate exposure sources can aid in targeting efforts to reduce exposure and improve public health.

DISCLAIMER

The findings and conclusions in this study are those of the authors and do not necessarily represent the official views or positions of the US Centers for Disease Control and Prevention. Use of trade names and commercial sources is for identification only and does not constitute endorsement by the US Department of Health and Human Services, or the US Centers for Disease Control and Prevention.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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