Science in One Health 3 (2024) 100062

Contents lists available at ScienceDirect

Science in One Health

journal homepage: www.journals.elsevier.com/science-in-one-health

Full length article

Dietary exposure assessment of perchlorate and chlorate in infant formulas marketed in Shanghai, China

Shenghao Yu [a], Yonghui Ge [a], Lujing Zhang [a], Yiqi Li [a], Wen Zhang [b], Chang Liu [c,**,1], Shaojie Peng [a,*,1]

[a] Information Application Research Center of Shanghai Municipal Administration for Market Regulation, Shanghai 200030, China
[b] Shanghai Institute of Quality Inspection and Technical Research, Shanghai 200233, China
[c] Department of Immunology and Microbiology, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China

ARTICLE INFO

Keywords:
Infant formulas
Perchlorate
Chlorate
Risk monitoring
Exposure assessment

ABSTRACT

Perchlorate and chlorate are ubiquitous pollutants that can adversely affect the thyroid function in humans. This study assessed the potential health risks associated with the dietary exposure of infants and young children to perchlorate and chlorate present in infant formulas available in Shanghai. The assessment was based on risk monitoring data from 150 samples of infant formulas in Shanghai between 2020 and 2022, along with the dietary consumption data of infants and young children. The detection rates of perchlorate and chlorate in infant formulas were 46.0% and 98.7%, with mean contents of 9.98 μg/kg and 112.01 μg/kg, and the maximum values of 151.00 μg/kg and 1475.00 μg/kg, respectively. The mean and 95th percentile (P_{95}) values of daily perchlorate exposure of 0–36-month-old infant and young children via infant formulas were 0.07 and 0.17 μg/kg body weight (bw) per day, respectively, which were lower than the tolerable daily intake (TDI) of perchlorate (0.3 μg/kg bw per day). The mean and P_{95} values of chlorate exposure via infant formulas in 0–36-month-old infants and young children were 0.83 and 1.89 μg/kg bw per day, which were lower than the TDI of chlorate (3 μg/kg bw per day). The P_{95} exposure of different age groups (0–6 months, 7–12 months and 13–36 months) of infants and young children to perchlorate and chlorate in infant formulas was below the TDI. Therefore, the risk associated with the exposure of 0–36-month-old infants and young children to perchlorate and chlorate from infant formulas in Shanghai is considered acceptable. Prioritizing environmental pollution control efforts to reduce the levels of perchlorate and chlorate in food products is important to safeguard the health of the infants and children under the One Health concept.

1. Introduction

Perchlorate is a persistent environmental pollutant with stable chemical properties, strong oxidizing properties and poor environmental degradability [1,2]. It is widely used to manufacture solid rocket propellants, ammunition, fireworks, road flares, rubber products, dye coatings, magnesium batteries and airbag inflators and for smelting [3–5]. Perchlorate contamination is found in water and various foods, such as dairy products, infant formulas, eggs, fruits, vegetables, meat, aquatic products, grains, tea, beverages [6–11], and even in breast milk, blood and saliva [12,13]. Humans are primarily exposed to perchlorate via the consumption of contaminated food and drinking water [14,15]. Perchlorate is quickly absorbed through the gastrointestinal tract and is distributed throughout the body in both humans and animals. It is mainly excreted through urine, with a smaller portion being excreted through feces [16,17]. Perchlorate inhibits the absorption of iodine by the thyroid gland, which affects the synthesis and release of thyroxine and leads to hypothyroidism, affecting the normal metabolism, growth, and development of the human body, especially those in infants, children and pregnant women [18–20].

Chlorate is a class of chlorine-containing anionic inorganic compounds with strong oxidizing properties. It is widely used in dyeing, printing, medicine, paper-making, tanning, ore treatment, bromine extraction from seawater, and as an agricultural herbicide [21,22]. Additionally, it is also a by-product of the disinfection of drinking water, food production water, and production and processing equipment with chlorine-containing disinfectants (including chlorine, chlorine dioxide or

---

* Corresponding author.
** Corresponding author.
E-mail addresses: tiantianlc@sjtu.edu.cn (C. Liu), pengshaojie2008@qq.com (S. Peng).
[1] These authors have contributed equally to this work.

https://doi.org/10.1016/j.soh.2024.100062
Received 17 November 2023; Accepted 19 January 2024

hypochlorite, etc) [23]. Chlorate is widely found in vegetables, fruits, dairy products, meat, grains, tea, infant formulas, supplementary foods for infants and young children, and even in breast milk [9,13,23,24]. Food and drinking water arethe primary routes of human exposure to chlorate [23,24]. Chlorate is rapidly absorbed after oral ingestion, and is widely distributed throughout the body's tissues [22,23]. Chlorate is excreted mainly through urine [23]. The thyroid gland and hematological system are the main targets of chlorate toxicity [23,25]. Acute chlorate toxicity induces methemoglobinemia, lysis of red blood cells, hemolytic anemia, and impairment of renal function [23,26]. Chlorate interferes with iodine absorption by the human thyroid gland, leading to decreased thyroid hormone synthesis, which may negatively affect brain development in infants and young children [23,25].

According to Chinese customs data, the import volume of infant formulas in China increased from 36,000 tons to 335,000 tons from 2008 to 2020, with an average annual growth rate of 20.4% [27]. The annual production of infant formulas in China during 2017 and 2019 was 600,000 and 650,000 tons [27]. Infant formulas are an important source of nutrition for non-breast-fed infants and young children [28,29]. Infant formulas made from raw milk (such as cow milk and goat milk) are a key concern in various countries. Perchlorate and chlorate from the environment not only affect animal health through feed and water [16,23,30], but also have a health impact on infants and young children through infant formulas and drinking water [28,31]. To address the challenges at the intersection of human (especially infants and young children), animal, and environmental health, the “One Health” method has been recently employed to study the relationship between environmental pollutants in food and human health [32].

In recent years, several studies have been conducted to evaluate dietary exposure to perchlorate and chlorate in infants and young children in different countries, such as the United States [33], China [13], and France [34]. In May 2023, the European Commission issued Regulation (EU) 2023/915 on maximum levels for certain contaminants in food, which repealed European Regulation (EC) No 1881/2006 and set a limit of 0.01 mg/kg for perchlorate in infant formula (ready-to-eat) [35]. However, there are no limiting standards for perchlorate and chlorate levels in infant formulas in other regions except European Commission. Standards for drinking water quality (Standardization Administration of China, GB 5749—2022) for perchlorate and chlorate in drinking water are set at 0.07 mg/L and 0.7 mg/L [36].

In this study, the risk of chronic dietary exposure to perchlorate and chlorate in 0–36-month-old infants and young children through infant formulas in Shanghai was assessed using a simple distribution assessment method. This study provides a reference for the standard formulation and the safety supervision of perchlorate and chlorate in infant formulas. This is the first risk assessment of perchlorate and chlorate contamination in infant formulas in Shanghai, a large international metropolis with 24 million permanent residents.

2. Methods

2.1. Sample collection

A total of 150 infant formula samples sold in Shanghai from 2020 to 2022 were monitored, including 50 samples of stage 1 for 0–6-month-old infants, 50 samples of stage 2 for 6–12-month-old infants, and 50 samples of stage 3 for 13–36-month-old young children. Samples were randomly collected from mother and baby stores and supermarkets in Shanghai. The places of origin included 13 provinces, autonomous regions, and municipalities directly under the Central Government, including Shanghai, Heilongjiang, Zhejiang, Shaanxi, Hebei, Shandong, Jiangsu, Gansu, Inner Mongolia, Guangdong, Jiangxi, Hunan and Liaoning and 12 foreign countries, including the Netherlands, Denmark, Germany, Australia, New Zealand, Ireland, the United Kingdom, Switzerland, France, Spain, South Korea and Singapore. In total, 52 manufacturers of 41 brands of infant formulas were involved.

2.2. Determination of chlorate and perchlorate levels in infant formulas using liquid chromatography-tandem mass spectrometry

The Shanghai Institute of Quality Supervision Inspection and Technical Research was contracted to test perchlorate and chlorate levels in the infant formulas. The test method, BJS 201706, “Determination of chlorate and perchlorate in food” was employed, which has been recognized by the former China Food and Drug Administration [37]. The following methodology was employed: after extraction and centrifugation of the infant formula sample, the supernatant was purified by a solid-phase extraction column and quantified by liquid chromatography-tandem mass spectrometry (LC-MS/MS) using an internal standard.

The standard products of chlorate and perchlorate were purchased from Sigma-Aldrich (St. Louis, MO, USA). Chlorate-$^{18}O_3$ and perchlorate-$^{18}O_4$ were purchased from Cambridge Isotope Laboratories, Inc (Tewksbury, MA, USA). HPLC grade formic acid (FA), acetonitrile (ACN), and methanol were obtained from Merck (Darmstadt, Germany). LC-MS/MS-grade ammonium formate (AF) was purchased from Merck (Darmstadt, Germany). Milli-Q quality water (18.2 MΩ·cm) was utilized throughout the study (Millipore, Billerica, MA, USA).

Samples were prepared by weighing 2.0 g of infant formula into a 50 mL polypropylene tubes. All tubes received 150 μL of the intermediate internal standard solution (1500 ng/mL for chlorate-$^{18}O_3$, 200 ng/mL for perchlorate-$^{18}O_4$). Add 5 mL of 0.1% acetic acid to water and 9 mL of methanol. The mixture was vigorously shaken for 5 min. After centrifugation at 10,000 r/min for 10 min (Thermo Fisher SL 16R, Waltham, MA, USA), the supernatant was filtered through PRiMEHLB (3 cc, 150 mg, Waters, MA, USA) and 0.22 μm organic filter membrane, consecutively, prior to injecting into the LC-MS/MS system. The internal standard approach was used for quantification..

A Masslynx V4.1 system coupled to a Waters TQ-XS mass spectrometer (Waters, MA, USA) was utilized. Analytes were separated on an Acclaim^{TM} Trinity^{TM} P1 Column (3 μm, 2.1 mm × 100 mm). The mobile phases was composed of acetonitrile (A) and a 20 mmol/L ammonium formate solution (B) with gradient elution at a flow rate of 0.5 mL/min. The gradient elution procedures are presented in Table 1. The optimized parameters for multiple reaction monitoring (MRM) mode and negative (ESI-2.0 kV) electrospray ionization modes using mass spectrometry were source temperature 150 °C, desolvation temperature 500 °C, cone voltage 30 V, cone hole gas flow 300 L/h, desolvation gas flow 700 L/h, nebulizer gas flow 4.00 bar. The column was maintained at 35 °C. Nitrogen gas was used. The LC-MS/MS acquisition parameters are listed in Table 2.

The isotope internal standard method was used to correct for matrix effects. A linear equation was fitted with the concentration as x-axis and the ratio of peak area of the native compound to the internal standard as y-axis and used for quantification of the results. For recoveries, the spiked concentrations were as follows: chlorate, 15, 30 and 150 μg/kg; perchlorate, 7.5, 15 and 75 μg/kg. The validation details are listed in Table 3.

2.3. Food consumption survey

The Fudan University School of Public Health was approached to investigate the food consumption in 0–36-month-old infants and young children in Shanghai. The consumption survey plan for infant formulas in

Table 1
Conditions of gradient elution. The mobile phases A was acetonitrile and mobile phase B was 20 mmol/L ammonium formate solution.

Time (min)	Mobile phase A (%)	Mobile phase B (%)
0	70	30
0.2	70	30
3.0	90	10
7.0	90	10
8.0	70	30
10.0	70	30

Table 2
LC-MS/MS parameters for the analysis of perchlorate and chlorate.

Compound	Retention time (min)	Parent Ion (*m/z*)	Product Ion (*m/z*)	Collision energy (eV)
Chlorate	4.51	83.0	67.0	15
		85.0	69.0	15
Perchlorate	2.38	99.0	83.0	18
		101.0	85.0	18
Chlorate-$^{18}O_3$	4.51	89.0	71.0	15
Perchlorate-$^{18}O_4$	2.38	107.0	89.0	18

Shanghai was reviewed and approved by the Academic Committee of Information Application Research Center of Shanghai Municipal Administration for Market Regulation. The survey was conducted from November 2022 to May 2023 at 16 Community Health Service Centers of the Child Health Clinic and Planned Immunization Clinic in the Putuo and Songjiang districts of Shanghai. The survey, which was conducted using a 24-h dietary recall method included basic information about infants and young children (such as gender, age, and weight) and the consumption of various foods by infants and young children (such as infant formulas, supplementary foods for infants and young children, etc.). The guardians of the infants and young children completed the dietary survey questionnaire. A total of 846 infants and children were interviewed, of whom 640 (327 males and 313 females) had consumed infant formulas, and the consumption rate was 75.7% (640/846).

2.4. Dietary exposure assessment

A simple distribution assessment method [28] was used to estimate the dietary exposure to perchlorate and chlorate in infant formulas, and the exposure was calculated as:

$$\text{Exp} = \frac{\text{F} \times \text{C}}{\text{bw} \times 1000}$$

where Exp is the daily dietary exposure of individual infants to perchlorate or chlorate, μg/kg body weight (bw) per day; F is the daily consumption of infant formula for individual infants, g/day; C is the mean content of perchlorate or chlorate in infant formula, μg/kg; and bw is the body weight of the individual, kg.

Based on the consumption patterns of infant formula in 0–36-month-old infants and young children, infants and children were divided into three groups, 0–6-month-old infants, 7–12-month-old infants and 13–36-month-old young children. Exposure to perchlorate or chlorate for infants and children aged 0–6 months, 7–12 months, 13–36 months and 0–36 months was calculated using the mean content of perchlorate or chlorate content in stage 1, stage 2, stage 3 and all infant formulas, respectively, and the individual consumption of infant formula.

2.5. Health-based guidance values

The National Research Council developed a reference dose (RfD) for perchlorate of 0.7 μg/kg bw per day in 2005 [38]. The U.S. Environmental Protection Agency also developed a RfD for perchlorate of 0.7 μg/kg bw per day in 2005 [39]. In 2011, Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Committee on Food Additives (JECFA) set a provisional maximum tolerable daily intake of 0.01 mg/kg bw per day for perchlorate [40]. In 2014, the European Food Safety Authority (EFSA) determined a TDI for perchlorate of 0.3 μg/kg bw per day [16].

In 2007, JECFA established an acceptable daily intake of 0–0.01 mg/kg bw per day for chlorate [41]. However, in 2015, EFSA considered the TDI for chlorate to be 3 μg/kg bw per day [23].

Based on the principle of maximum protection, the strictest health guideline values established by the EFSA were adopted in this study to assess the risk of dietary exposure of infants and young children to perchlorate and chlorate via infant formulas.

2.6. Statistical analysis

In this study, not detected (ND) was treated according to the “Recommendations for credible evaluation of low-level contaminants in food” principle proposed at the second GEMS/FOOD meeting [42], i.e., if the proportion of samples with non-detected data was ≤60% of the total sample size, all ND values were replaced by 1/2 of LOD. Statistical analysis was performed by using IBM SPSS Statistics 28.0 software (International Business Machines corporation, New York, USA). Spearman correlation analysis was used to study the correlation between the perchlorate and chlorate content levels in the samples. The perchlorate and chlorate contents in the infant formula samples showed a non-normal distribution. The Mann-Whitney *U* test was used to analyze the differences of perchlorate or chlorate content levels in different production locations (domestic and imported) and different types of samples (infant cow formulas and infant goat formulas). The Kruskal-Wallis *H* test was used to analyze the differences in perchlorate or chlorate content levels at different stages of the samples. The Kruskal-Wallis *H* test was used to analyze the differences in perchlorate or chlorate exposure in different age groups. $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. General information

The overall detection rate of perchlorate in commercially sold infant formulas in Shanghai from 2020 to 2022 was found to be 46.0% (69/150), with a mean content of 9.98 μg/kg, a median value of 1.50 μg/kg, and a maximum value of 151.00 μg/kg. The detection rate of chlorate was 98.7% (148/150), the mean content was 112.01 μg/kg, the median value was 56.10 μg/kg, and the maximum value was 1475.00 μg/kg (shown in Table 4). Based on the the statistical analysis, no correlation was observed between perchlorate and chlorate contents in infant formulas ($r = 0.027$, $P > 0.05$).

3.2. Perchlorate and chlorate levels at different stages of infant formulas

The detection rates of perchlorate in stage 1, 2, and 3 infant formulas were 44.0% (22/50), 44.0% (22/50) and 50.0% (25/50), respectively. The mean perchlorate concentrations in infant formulas at stages 1, stage 2 and stage 3 were 9.31, 7.90 and 12.73 μg/kg, respectively. Difference in the perchlorate content among the samples from different stages was not significant ($P > 0.05$).

Table 3
Overview of the methodological characteristics including linearity range, correlation coefficient (R^2), limit of detection (LOD); limit of quantification (LOQ), recovery and relative standard deviation (RSD).

Compound	Linearity range (μg/L)	Correlation coefficient (R^2)	LOD (μg/kg)	LOQ (μg/kg)	Average recovery ± RSD (%, $n = 6$)		
					Spiked low	Spiked middle	Spiked high
Chlorate	2–200	0.9998	4.5	15.0	89.8±6.5	99.3±9.3	101.0±3.1
Perchlorate	1–100	0.9998	3.0	7.5	85.1±13.8	97.4±10.9	97.6±1.4

Note: n=6 indicates conducting 6 parallel experiments at the same concentration level, and calculating the average recovery and relative standard deviation for each concentration level separately.

Table 4
Detection of perchlorate and chlorate in infant formulas from 2020 to 2022.

Compound	Number of samples	Detection rate (%)	Content (μg/kg)				
			Mean	Standard deviation	Median	P_{95}	Maximum
Perchlorate	150	46.0	9.98	20.63	1.50	42.56	151.00
Chlorate	150	98.7	112.01	157.04	56.10	358.45	1475.00

Note: P_{95} is the 95th percentile.

The detection rates of chlorate in infant formulas at stages 1, 2 and 3 were 98.0% (49/50), 98.0% (49/50) and 100%, respectively. The mean concentrations of chlorate in the infant formulas at stages 1, 2, and 3 were 107.29, 129.64 and 99.10 μg/kg, respectively. No significant difference was noted in chlorate content among the samples from the different stages ($P > 0.05$). As shown in Table 5.

3.3. Perchlorate and chlorate in infant formulas from different production locations

The perchlorate detection rates in domestic and imported infant formulas were 57.3% (43/75) and 34.7% (26/75), respectively. The mean content of perchlorate in domestic infant formulas (13.17 μg/kg) was higher than that in imported infant formulas (6.80 μg/kg). Additionally, the median perchlorate concentration in domestic infant formulas (6.03 μg/kg) was higher than that in imported formulas (1.50 μg/kg). Difference in the perchlorate content between the domestic and imported samples was significant ($P < 0.05$).

The detection rates of chlorate in domestic and imported infant formulas were 100% and 97.3% (73/75), respectively. The mean concentrations of chlorate in domestic and imported infant formulas were 124.84 μg/kg and 99.17 μg/kg; the median values were 63.90 μg/kg and 45.40 μg/kg, respectively. There was a significant difference in the chlorate content between the domestic and imported samples ($P< 0.05$) (Table 6).

3.4. Perchlorate and chlorate in different types of infant formulas

The detection rates of perchlorate in infant cow formulas and infant goat formulas were 44.4% (55/124) and 53.8% (14/26); the mean contents were 7.96 μg/kg and 19.61 μg/kg; the median values were 1.50 μg/kg and 5.13 μg/kg, respectively. There was no statistical difference in perchlorate content between infant cow formulas and infant goat formulas ($P > 0.05$).

Chlorate were detected in 98.4% (122/124) of infant cow formulas (median: 52.25 μg/kg, mean: 109.54 μg/kg) and 100% of infant goat formulas (median: 76.60 μg/kg, mean: 123.78 μg/kg). The differences in chlorate concentrations among the different sample types were not statistically significant ($P > 0.05$). As shown in Table 7.

3.5. Daily consumption of infant formulas

The mean and P_{95} values for daily consumption of infant formulas for 0–36-month-old infants and young children in Shanghai were 73.2 and 137.9 g/day, respectively. The mean daily consumption varies by age group: 82.1 g/day for 0–6-month-old infants, 90.7 g/day for 7–12-month-old infants, and 62.3 g/day for 13–36-month-old young children. The P_{95} values for each group were 150.1, 153.6 and 108.6 g/day, respectively (shown in Table 8).

3.6. Dietary exposure assessment

For 0–36-month-old infants and young children in Shanghai, the mean and P_{95} values of daily perchlorate exposure were 0.07 and 0.17 μg/kg bw per day, accounting for 23.3% and 56.7% of the TDI (0.3 μg/kg bw per day), respectively. Approximately 0.3% of infants and children were exposed to perchlorate above the TDI. When analyzed by age group, the mean exposure to perchlorate was 0.11, 0.07, and 0.06 μg/kg bw per day for infants and children aged 0–6 months, 7–12 months and 13–36 months, and the P_{95} exposure for these groups was 0.22, 0.13 and 0.12 μg/kg bw per day. The mean and P_{95} values for daily perchlorate exposure in all age groups were below the TDI. Overall, differences in daily perchlorate exposure between infants and young children of different age groups (0–6 months, 7–12 months and 13–36 months) was significant ($P < 0.05$). Exposure decreased in the following order: infants aged 0–6 months, infants aged 7–12 months, and children aged 13–36 months. The health risks of daily exposure via infant formulas in 0–36-month-old infants and young children in Shanghai were acceptable. However, 0.9% of 0–6-month-old infants had higher perchlorate exposure than the TDI, and the health risks of perchlorate exposure in 0–6-month-old infants remains to be considered. The results are presented in Table 9 and Fig. 1.

The mean and P_{95} values of daily chlorate exposure from infant formulas in 0–36-month-old infants and young children in Shanghai were 0.83 and 1.89 μg/kg bw per day, accounting for 27.7% and 63.0% of the TDI (3 μg/kg bw per day), respectively. Only 0.5% of infants and children were exposed to chlorate above the TDI. When analyzed by age group, the mean chlorate exposure was 1.32, 1.20 and 0.50 μg/kg bw per day for infants and children aged 0–6 months, 7–12 months and 13–36 months, and the P_{95} exposure was 2.52, 2.14 and 0.92 μg/kg bw per day. The mean and P_{95} values of the daily chlorate exposure were below the TDI for all age groups. Overall, there was a significant difference in daily chlorate exposure among infants and young children in the different age groups (0–6 months, 7–12 months and 13–36 months) ($P < 0.05$). The daily chlorate exposure of 0–6 months infants and 7–12 months infants was higher than that of children aged 13–36 months ($P < 0.05$). Difference in the daily chlorate exposure was not significant between infants aged 0–6 months and the infants aged 7–12 months ($P > 0.05$). The health risks of

Table 5
Detection results of perchlorate and chlorate in different stages of infant formulas.

Compound	Stage	Number of samples	Detection rate (%)	Content (μg/kg)				
				Mean	Standard deviation	Median	P_{95}	Maximum
Perchlorate	Stage 1	50	44.0	9.31	17.86	1.50[a]	45.80	109.00
	Stage 2	50	44.0	7.90	17.22	1.50[a]	34.55	114.10
	Stage 3	50	50.0	12.73	25.81	2.70[a]	65.88	151.00
Chlorate	Stage 1	50	98.0	107.29	126.03	46.95[a]	461.25	521.00
	Stage 2	50	98.0	129.64	219.05	65.10[a]	413.35	1475.00
	Stage 3	50	100	99.10	103.04	55.00[a]	339.30	387.00

Note: The same lowercase letters on shoulder markers in the same column indicate no significant differences ($P > 0.05$), whereas different lowercase letters in the same column indicate significant differences ($P < 0.05$). The same applies below.

Table 6
Detection results of perchlorate and chlorate in infant formulas from different production locations.

Compound	Place of production	Number of samples	Detection rate (%)	Content (μg/kg)				
				Mean	Standard deviation	Median	P_{95}	Maximum
Perchlorate	Domestic	75	57.3	13.17	23.23	6.03^{a}	44.50	151.00
	Imported	75	34.7	6.80	17.22	1.50^{b}	33.32	109.00
Chlorate	Domestic	75	100	124.84	188.52	63.90^{a}	377.20	1475.00
	Imported	75	97.3	99.17	117.40	45.40^{b}	363.80	536.00

Note: The same lowercase letters on the shoulder markers in the same column indicate no significant differences ($P > 0.05$), while different lowercase letters in the same column indicate significant differences ($P < 0.05$).

Table 7
Detection results of perchlorate and chlorate in different types of infant formulas.

Compound	Type of milk powder	Number of samples	Detection rate (%)	Content (μg/kg)				
				Mean	Standard deviation	Median	P_{95}	Maximum
Perchlorate	Infant cow formula	124	44.4	7.96	15.12	1.50^{a}	37.53	109.00
	Infant goat formula	26	53.8	19.61	35.99	5.13^{a}	138.09	151.00
Chlorate	Infant cow formula	124	98.4	109.54	166.18	52.25^{a}	380.00	1475.00
	Infant goat formula	26	100	123.78	104.62	76.60^{a}	323.65	324.00

Note: The same lowercase letters on the shoulder markers in the same column indicate no significant differences ($P > 0.05$), while different lowercase letters in the same column indicate significant differences ($P < 0.05$).

Table 8
Daily consumption of infant formula for infants and young children in Shanghai.

Age group (month)	Number of surveys	Body weight (kg)	Consumption (g/day)					
			Mean	Standard deviation	Median	P_{95}	$P_{97.5}$	Maximum
0–6	117	7.0	82.1	42.7	86.0	150.1	166.7	180.0
7–12	164	10.0	90.7	38.3	89.0	153.6	167.7	200.0
13–36	359	12.9	62.3	25.3	60.8	108.6	118.8	169.0
Total	640	11.0	73.2	35.0	69.6	137.9	149.9	200.0

Table 9
Daily exposure levels of perchlorate and chlorate from infant formulas for infants and young children aged 0–36 months in Shanghai.

Compound	Age group (month)	Daily exposure (μg/kg bw per day)				Ratio of daily exposure to TDI (%)				Percentage exceeding TDI (%)
		Mean	Median	P_{95}	Maximum	Mean	Median	P_{95}	Maximum	
Perchlorate	0–6	0.11	0.11^{a}	0.22	0.37	36.7	36.7	73.3	123.3	0.9
	7–12	0.07	0.07^{b}	0.13	0.16	23.3	23.3	43.3	53.3	0.0
	13–36	0.06	0.06^{c}	0.12	0.15	20.0	20.0	40.0	50.0	0.0
	0–36	0.07	0.06	0.17	0.40	23.3	20.0	56.7	133.3	0.3
Chlorate	0–6	1.32	1.28^{a}	2.52	4.29	44.0	42.7	84.0	143.0	1.7
	7–12	1.20	1.19^{a}	2.14	2.59	40.0	39.7	71.3	86.3	0.0
	13–36	0.50	0.47^{b}	0.92	1.20	16.7	15.7	30.7	40.0	0.0
	0–36	0.83	0.69	1.89	4.48	27.7	23.0	63.0	149.3	0.5

Note: The same lowercase letters on the shoulder markers in the same column indicate no significant differences ($P > 0.05$), while different lowercase letters in the same column indicate significant differences ($P < 0.05$).

daily exposure to chlorate via infant formulas for 0–36-month-old infants and young children in Shanghai were acceptable. However, chlorate exposure in 1.7% of 0–6-month-old infants was higher than the TDI, and the health risks of chlorate exposure in 0–6-month-old infants remains to be considered. The results are presented in Table 9 and Fig. 2.

4. Discussion

The intake of feed and water contaminated with perchlorate and chlorate by cows and goat may lead to the contamination of cow and goat milk with perchlorate and chlorate [30,43,44]. Cow and goat milk are important raw materials for infant formulas. If cow and goat milk are contaminated with perchlorate and chlorate, it is difficult to remove them during production and processing, leading to residual perchlorate and chlorate in infant formulas [44–46]. In addition, the use of chlorinated disinfectants in the production process of infant formulas to clean and disinfect pipes and processing equipment during the production process can also result in chlorate residues [24,28,46].

The detection rates of perchlorate and chlorate in the infant formulas marketed in Shanghai were 46.0% and 98.7%, respectively, indicating that perchlorate and chlorate migrated through the food chain and ultimately leading to perchlorate and chlorate contamination in infant formulas. The mean concentration of perchlorate in infant formulas in our study (9.98 μg/kg) was close to that in the 278 infant formulas sold in China (10.9 μg/kg) reported by Liu et al. [28], and it was lower than the mean value of perchlorate in 31 commercially available infant formulas in Wuhan, China (18.44 μg/kg) reported by Liu et al. [31], and much higher than the mean value of perchlorate in 53 infant formulas sold in Guangzhou and Shenzhen, China (1.14 μg/kg) reported by Li et al. [13]. A study [45] reported that the mean value of perchlorate in 26 marketed infant formulas in Republic of Korea was 7.83 μg/kg, which was lower than that reported by our study. The mean concentration of chlorate in

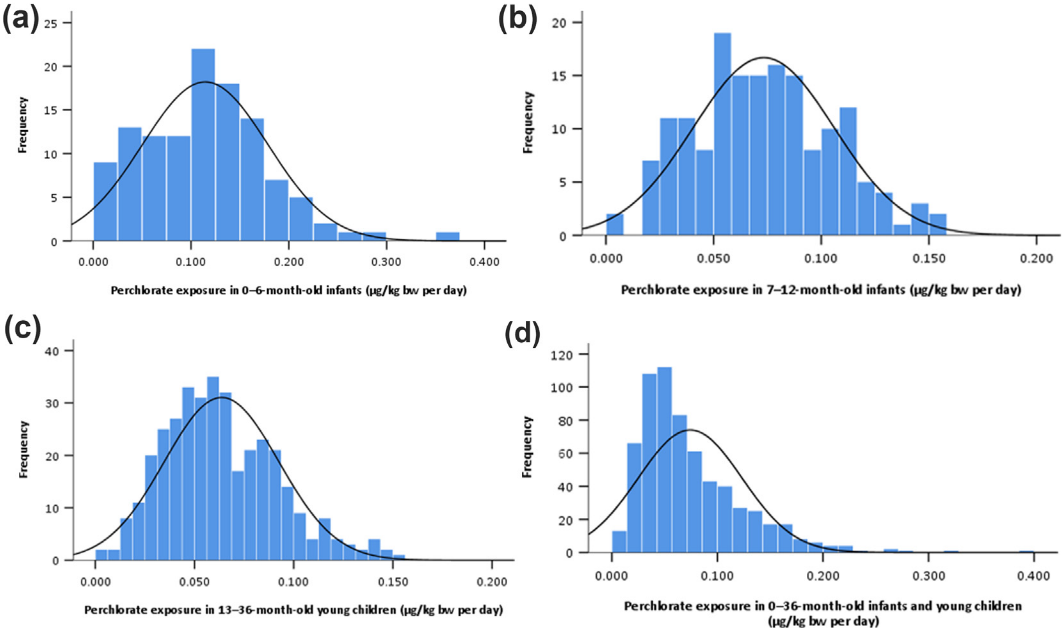

Fig. 1. Distribution of daily perchlorate exposure from infant formulas for infants and young children aged 0–36 months.

our study (112.01 μg/kg) was lower than that reported by Liu et al. [28] in 278 infant formulas (138.03 μg/kg), and much higher than that reported by Li et al. [13] in 53 infant formulas (6.54 μg/kg). The perchlorate and chlorate contents in infant formulas vary across studies, possibly due to differences in the source and brand of the samples in these studies [13,28,31,45].

The mean exposure of perchlorate via infant formulas for infants aged 0–6 months, 7–12 months and 13–36 months in Shanghai was 0.11, 0.07 and 0.06 μg/kg bw per day, respectively, which were lower than the mean exposure of infants to perchlorate via infant formulas in China reported by Liu et al. [28] (0–6 months: 0.114 μg/kg bw per day, 7–12 months: 0.105 μg/kg bw per day, and 13–36 months: 0.070 μg/kg bw per day). Li et al. [13] reported that the mean perchlorate exposure of infants in different age groups (0–6 months, 6–12 months and 12–24 months) through infant formulas in China was 0.150, 0.151 and 0.161 μg/kg bw per day, respectively. Liu et al. [31] reported that the mean perchlorate exposure of infants in different age groups (0–6 months, 7–12 months and 13–36 months) through infant formula in China was 0.31, 0.26 and 0.16 μg/kg bw per day, respectively, while the mean perchlorate exposure for infants (ages 1–377 days) in the USA was 0.208 μg/kg bw per day, as reported by Valentín-Blasini et al. [33].

The mean chlorate exposure via infant formulas for infants aged 0–6 months, 7–12 months, and 13–36 months in Shanghai was 1.32, 1.20 and 0.50 μg/kg bw per day. Liu et al. [28] reported that the mean chlorate exposure in infants and young children of different age groups was 1.901, 1.115 and 0.720 μg/kg bw per day (0–6 months, 7–12

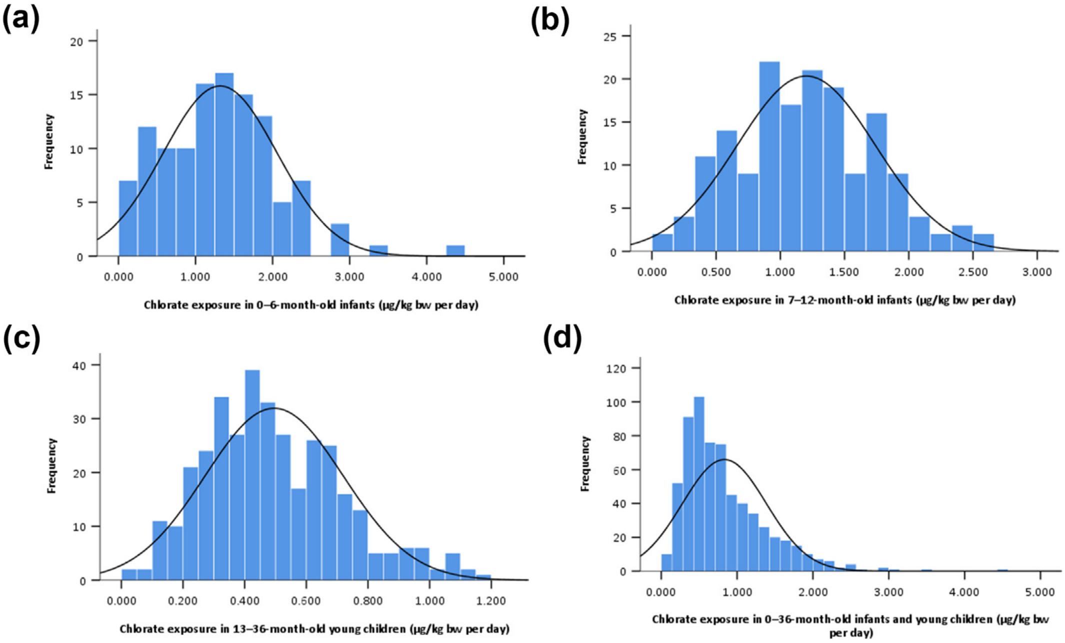

Fig. 2. Distribution of daily chlorate exposure from infant formulas for infants and young children aged 0–36 months.

months and 13–36 months). Li et al. [13] reported that the mean chlorate exposure in infants and young children of different age groups (0–6 months, 6–12 months and 12–24 months) was 0.110, 0.110 and 0.117 μg/kg bw per day. Differences in the perchlorate and chlorate exposure in infants and young children in different studies are mainly related to the pollution levels of the perchlorate and chlorate in infant formulas in different regions and the consumption of infant formulas [28,31,33].

There was also some uncertainties in this study, as follows: First, the sample size ($n = 150$) was small, which resulted in a lack of strong representation. Second, exposure to perchlorate and chlorate in other food products (such as infant complementary foods), water, and breast milk was not considered in this study, which may have led to some degree of underestimation. Third, a simple distribution assessment method was used, and chronic dietary exposure was based on the mean content of the perchlorate or chlorate, rather than the upper limit of the perchlorate or chlorate content (e.g. P_{95}), which may result in an underestimation.

The “One Health” approach is applied to ensure animal health, food safety, and human health through comprehensive prevention and measures which reduce pollution of perchlorate and chlorate in the environment, animals, plants and food. Based on our results, the following countermeasures can be implemented: First, the perchlorate and chlorate emissions from industrial enterprises should be strictly controlled to reduce environmental pollution and the migration of perchlorate and chlorate into plants and animals. Methods such as chemical remediation and bioremediation are recommended to reduce perchlorate and chlorate pollution in water and soil. Second, infant formula manufacturers should strictly implement their primary responsibility of food safety. Infant formula manufacturers should strengthen the pollution detection and risk prevention and control of perchlorate and chlorate. Therefore, it is critical to choose raw and auxiliary materials with low perchlorate and chlorate contents. Dairy farms and infant formula manufacturers should reduce the use of chlorine-containing disinfectants or use alternative types of disinfectants to reduce the pollution level of chlorate in infant formulas. Third, government agencies should improve the monitoring of perchlorate and chlorate risks in infant formulas and consistently collect relevant data. Studies should also be conducted on the risk assessment, control standards and limit standards for perchlorate and chlorate in infant formulas. Fourth, scientific research institutions should strengthen research on the migration and transformation of perchlorate and chlorate into the environment, plants, animals, and food.

Authors' contributions

SH-Y and YH-G drafted the manuscript. SJ-P, C-L, YQ-L, LJ-Z and W-Z revised the manuscript. All the authors have read and approved the final version of the manuscript.

Funding statement

This project was supported by Science and Technology Project of Shanghai Municipal Administration for Market Regulation in 2022 (No. 2022-67).

Data availability statement

Please contact the corresponding author for data requests.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that can have appeared to influence the work reported in this paper.

Acknowledgements

None.

References

[1] Y. Erdemgil, T. Gözet, Ö. Can, İ. Ünsal, A. Özpınar, Perchlorate levels found in tap water collected from several cities in Turkey, Environ. Monit. Assess. 188 (3) (2016) 158, https://doi.org/10.1007/s10661-016-5161-2.

[2] P. Kumarathilaka, C. Oze, S.P. Indraratne, M. Vithanage, Perchlorate as an emerging contaminant in soil, water and food, Chemosphere 150 (2016) 667–677, https://doi.org/10.1016/j.chemosphere.2016.01.109.

[3] C.M. Steinmaus, Perchlorate in water supplies: sources, exposures, and health effects, Curr. Environ. Health Rep. 3 (2) (2016) 136–143, https://doi.org/10.1007/s40572-016-0087-y.

[4] C.W. Murray, S.K. Egan, H. Kim, N. Beru, P.M. Bolger, US food and Drug administration's total diet study: dietary intake of perchlorate and iodine, J. Expo. Sci. Environ. Epidemiol. 18 (6) (2008) 571–580, https://doi.org/10.1038/sj.jes.7500648.

[5] Z.W. Gan, H.W. Sun, R.N. Wang, Y.Y. Deng, Occurrence and exposure evaluation of perchlorate in outdoor dust and soil in mainland China, Sci. Total Environ. 470–471 (2014) 99–106, https://doi.org/10.1016/j.scitotenv.2013.09.067.

[6] R. Calderón, P. Palma, N. Arancibia-Miranda, U.J. Kim, E. Silva-Moreno, K. Kannan, Occurrence, distribution and dynamics of perchlorate in soil, water, fertilizers, vegetables and fruits and associated human exposure in Chile, Environ. Geochem. Health 44 (2) (2022) 527–535, https://doi.org/10.1007/s10653-020-00680-6.

[7] Y. Chen, Z. Zhu, X. Wu, D. Zhang, J. Tong, Y. Lin, et al., A nationwide investigation of perchlorate levels in staple foods from China: implications for human exposure and risk assessment, J. Hazard Mater. 439 (2022) 129629, https://doi.org/10.1016/j.jhazmat.2022.129629.

[8] S. Panseri, M. Nobile, F. Arioli, C. Biolatti, R. Pavlovic, L.M. Chiesa, Occurrence of perchlorate, chlorate and polar herbicides in different baby food commodities, Food Chem. 330 (2020) 127205, https://doi.org/10.1016/j.foodchem.2020.127205.

[9] P. Constantinou, D. Louca-Christodoulou, A. Agapiou, LC-ESI-MS/MS determination of oxyhalides (chlorate, perchlorate and bromate) in food and water samples, and chlorate on household water treatment devices along with perchlorate in plants, Chemosphere 235 (2019) 757–766, https://doi.org/10.1016/j.chemosphere.2019.06.180.

[10] J.W. Lee, S.H. Oh, J.E. Oh, Monitoring of perchlorate in diverse foods and its estimated dietary exposure for Korea populations, J. Hazard Mater. 243 (2012) 52–58, https://doi.org/10.1016/j.jhazmat.2012.09.037.

[11] M. Nobile, L. Danesi, R. Pavlovic, G. Mosconi, F. Di Cesare, F. Arioli, et al., Presence of chlorate and perchlorate residues in raw bovine milk from Italian farms, Foods 11 (18) (2022) 2741, https://doi.org/10.3390/foods11182741.

[12] K. Kannan, M.L. Praamsma, J.F. Oldi, T. Kunisue, R.K. Sinha, Occurrence of perchlorate in drinking water, groundwater, surface water and human saliva from India, Chemosphere 76 (1) (2009) 22–26, https://doi.org/10.1016/j.chemosphere.2009.02.054.

[13] M. Li, M. Xiao, Q. Xiao, Y. Chen, Y. Guo, J. Sun, et al., Perchlorate and chlorate in breast milk, infant formulas, baby supplementary food and the implications for infant exposure, Environ. Int. 158 (2022) 106939, https://doi.org/10.1016/j.envint.2021.106939.

[14] D.R. Huber, B.C. Blount, D.T. Mage, F.J. Letkiewicz, A. Kumar, R.H. Allen, Estimating perchlorate exposure from food and tap water based on US biomonitoring and occurrence data, J. Expo. Sci. Environ. Epidemiol. 21 (4) (2011) 395–407, https://doi.org/10.1038/jes.2010.31.

[15] G. Lisco, A. De Tullio, V.A. Giagulli, G. De Pergola, V. Triggiani, Interference on iodine uptake and human thyroid function by perchlorate-contaminated water and food, Nutrients 12 (6) (2020) 1669, https://doi.org/10.3390/nu12061669.

[16] EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain), Scientific opinion on the risks to public health related to the presence of perchlorate in food, in particular fruits and vegetables, EFSA J. 12 (10) (2014) 3869, https://doi.org/10.2903/j.efsa.2014.3869, 117.

[17] H.X. Chen, M.H. Ding, Y.G. Li, Q. Liu, K.L. Peng, Dose-Response relationship between orally administered ammonium perchlorate and urine perchlorate concentrations in rats: possible biomarker to quantify environmental ammonium perchlorate exposure on thyroid homeostasis, Arch. Environ. Occup. Health 70 (5) (2015) 286–290, https://doi.org/10.1080/19338244.2014.904265.

[18] M.A. Greer, G. Goodman, R.C. Pleus, S.E. Greer, Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans, Environ. Health Perspect. 110 (9) (2002) 927–937, https://doi.org/10.1289/ehp.02110927.

[19] M.V. Maffini, L. Trasande, T.G. Neltner, Perchlorate and diet: human exposures, risks, and mitigation strategies, Curr. Environ. Health Rep. 3 (2) (2016) 107–117, https://doi.org/10.1007/s40572-016-0090-3.

[20] R.C. Pleus, L.M. Corey, Environmental exposure to perchlorate: a review of toxicology and human health, Toxicol. Appl. Pharmacol. 358 (2018) 102–109, https://doi.org/10.1016/j.taap.2018.09.001.

[21] D.J. Smith, C.E. Oliver, J.B. Taylor, R.C. Anderson, Invited review: efficacy, metabolism, and toxic responses to chlorate salts in food and laboratory animals, J. Anim. Sci. 90 (11) (2012) 4098–4117, https://doi.org/10.2527/jas.2011-4997.

[22] S.N. Ali, H. Arif, A.A. Khan, R. Mahmood, Acute renal toxicity of sodium chlorate: redox imbalance, enhanced DNA damage, metabolic alterations and inhibition of brush border membrane enzymes in rats, Environ. Toxicol. 33 (11) (2018) 1182–1194, https://doi.org/10.1002/tox.22624.

[23] EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain), Scientific Opinion on risks for public health related to the presence of chlorate in food, EFSA J. 13 (6) (2015) 4135, https://doi.org/10.2903/j.efsa.2015.4135, 103.

[24] B. Kettlitz, G. Kemendi, N. Thorgrimsson, N. Cattoor, L. Verzegnassi, Y. Le Bail-Collet, et al., Why chlorate occurs in potable water and processed foods: a critical assessment and challenges faced by the food industry, Food Addit. Contam. Part A Chem. Anal. Control Expo. Risk Assess. 33 (6) (2016) 968–982, https://doi.org/10.1080/19440049.2016.1184521.

[25] M.J. Hooth, A.B. Deangelo, M.H. George, E.T. Gaillard, G.S. Travlos, G.A. Boorman, et al., Subchronic sodium chlorate exposure in drinking water results in a concentration-dependent increase in rat thyroid follicular cell hyperplasia, Toxicol. Pathol. 29 (2) (2001) 250–259, https://doi.org/10.1080/019262301317052530.

[26] S.N. Ali, M.K. Ahmad, R. Mahmood, Sodium chlorate, a herbicide and major water disinfectant byproduct, generates reactive oxygen species and induces oxidative damage in human erythrocytes, Environ. Sci. Pollut. Res. Int. 24 (2) (2017) 1898–1909, https://doi.org/10.1007/s11356-016-7980-7.

[27] Y.R. Tian, C. Zhang, H. Peng, X.X. Dong, New characteristics and trends of infant formula industry change in China, Food and Nutrition in China 27 (11) (2021) 14–19, https://doi.org/10.19870/j.cnki.11-3716/ts.20210625.002 (in Chinese).

[28] Q. Liu, W. Mao, D. Jiang, X. Yang, D. Yang, The contamination and estimation of dietary intake for perchlorate and chlorate in infant formulas in China, Food Addit. Contam. Part A Chem. Anal. Control Expo. Risk Assess. 38 (12) (2021) 2045–2054, https://doi.org/10.1080/19440049.2021.1973112.

[29] B. Başaran, The evaluation of childhood foods and infant formula exposure to furan, chloropropanols and acrylamide contamination by food processing, infant feeding - breast versus formula, Intech (2020), https://doi.org/10.5772/intechopen.93417.

[30] Q. Zhang, W.F. Mao, W.D. Guo, Y.X. Pu, K. Hou, Source analysis of chlorate and perchlorate pollution in liquid milk in a city, J. Food Saf. Qual. 12 (20) (2021) 7940–7945, https://doi.org/10.19812/j.cnki.jfsq11-5956/ts.2021.20.006 (in Chinese).

[31] X. Liu, H. Han, H. Xu, H. Zhang, M. Fang, Q. Wang, et al., Integration of probabilistic exposure assessment and risk characterization for perchlorate in infant formula and supplementary food, Food Chem. Toxicol. 168 (2022) 113347, https://doi.org/10.1016/j.fct.2022.113347.

[32] World Health Organization, Tripartite and UNEP Support OHHLEP's Definition of "One Health, 2021. https://www.who.int/news/item/01-12-2021-tripartite-and-unep-support-ohhlep-s-definition-of-one-health. (Accessed 10 June 2023).

[33] L. Valentín-Blasini, B C Blount, S. Otero-Santos, Y. Cao, J. C Bernbaum, W. J Rogan, Perchlorate exposure and dose estimates in infants, Environ. Sci. Technol. 45 (9) (2011) 4127–4132, https://doi.org/10.1021/es103160j.

[34] C. Vigreux-Besret, A. Mahé, G. Ledoux, A. Garnier, C. Rosin, A. Baert, et al., Perchlorate: water and infant formulae contamination in France and risk assessment in infants, Food Addit. Contam. Part A Chem. Anal. Control Expo, Risk Assess 32 (7) (2015) 1148–1155, https://doi.org/10.1080/19440049.2015.1036382.

[35] European Commission, Commission Regulation (EU) 2023/915 of 25 April 2023 on Maximum Levels for Certain Contaminants in Food and Repealing Regulation (EC) No 1881/2006, 2023. https://www.eurofins.de/food-analysis/food-news/food-testing-news/recast-of-ec-contaminants-regulation-no-1881-2006/. (Accessed 10 June 2023).

[36] State Administration for Market Regulation, Standardization Administration of China, Standards for Drinking Water Quality, GB 5749, 2022 (in Chinese).

[37] China Food and Drug Administration, Determination of Chlorate and Perchlorate in Food. BJS 201706 (in Chinese).

[38] National Research Council, Health Implications of Perchlorate Ingestion, 2005. https://nap.nationalacademies.org/resource/11202/perchlorate_brief_final.pdf. (Accessed 10 June 2023).

[39] U.S. Environmental Protection Agency, Perchlorate and Perchlorate Salts, 2005. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/1007_summary.pdf#nameddest=rfd. (Accessed 10 June 2023).

[40] Joint FAO/WHO Expert Committee on Food Additives, Evaluation of Certain Contaminants in Food: Seventy-Second Report of the Joint FAO/WHO Expert Committee on Food Additives (WHO Technical Report Series, no.959), 2011.

[41] Joint FAO/WHO Expert Committee on Food Additives, Evaluation of Certain Food Additives and Contaminants: Sixty-Eighth Report of the Joint FAO/WHO Expert Committee on Food Additives (WHO Technical Report Series, 2007 no.947).

[42] GEMS/Food-EURO, Second Workshop on Reliable Evaluation of Low-Level Contamination of Food: Report on a Workshop in the Frame of GEMS/Food-EURO, 2005. http://toolbox.foodcomp.info/References/LOD/GEMS-Food-EURO%20%20-%20%20Reliable%20Evaluation%20of%20Low-Level%20Contamination%20of%20Food.pdf. (Accessed 10 June 2023).

[43] C.P. Rice, R.L. Baldwin Vi, L.C. Abbott, C.J. Hapeman, A.V. Capuco, A. Le, et al., Predicting perchlorate exposure in milk from concentrations in dairy feed, J. Agric. Food Chem. 55 (21) (2007) 8806–8813, https://doi.org/10.1021/jf070953h.

[44] H.J. Chen, J. Kang, C. Fan, Y. Li, L.J. Zhang, L. Zhou, Analysis and screening of chlorate pollution in infant formula goat milk powder, Food Ind 44 (3) (2023) 64–69 (in Chinese).

[45] N. Her, J. Kim, Y. Yoon, Perchlorate in dairy milk and milk-based powdered infant formula in South Korea, Chemosphere 81 (6) (2010) 732–737, https://doi.org/10.1016/j.chemosphere.2010.07.031.

[46] L.Y. Li, C. Gao, X.J. Chu, X.P. Liu, J.C. Hua, H.Y. Zheng, Contamination status and sources of chlorate and perchlorate in infant formula milk powder, J. Dairy Sci. Technol. 46 (4) (2023) 28–34 (in Chinese).