Journal of Medical and Biological Engineering (2025) 45:826–832
https://doi.org/10.1007/s40846-025-00995-8

ORIGINAL ARTICLE

Chlorine Dioxide Medical Device Sterilization: Residual Toxicity Testing

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Received: 15 May 2025 / Accepted: 5 November 2025 / Published online: 2 December 2025

Abstract

Purpose Ethylene oxide (EtO), a commonly used sterilant for medical devices, is a known carcinogen that leaves carcinogenic residuals. Recent regulatory changes encourage medical device manufacturers to consider non-carcinogenic sterilants, including chlorine dioxide (ClO_2) sterilization. Although medical device manufacturers often request ClO_2 residual testing, there is a lack of literature exploring ClO_2 residual toxicity. This research bridges this gap by proposing testing criteria and assessing the toxicity of chlorite, chlorate, and chloride residuals post ClO_2 sterilization.

Methods We developed criteria using data from guidelines published by the United States Environmental Protection Agency and the World Health Organization. We completed a descriptive analysis of ion chromatography testing of different medical devices sterilized by ClO_2, including a device indicated for incidental contact, a device to treat corneal abrasions, a smoking cessation inhaler, a device to treat embolisms, polychlorotrifluoroethylene bottles, and prefilled syringes.

Results Results showed that the residual levels from each device tested were below toxicity limits of <6.83 mg/device or <0.8 mg/L for chlorite and <70.65 mg/device or <0.7 mg/L for chlorate. Chloride, a naturally occurring element considered non-toxic, was not included in the analysis.

Conclusion These results support ClO_2 sterilization as a viable, non-toxic alternative to EtO for medical device manufacturers and contract sterilizers. Future research is needed to determine residual toxicity criteria for high-contact medical devices intended for long-term use.

Keywords Chlorine dioxide · Medical device sterilization · Residual toxicity · Chlorate · Chlorite

1 Introduction

Many medical device manufacturers and contract sterilizers rely on ethylene oxide (EtO) sterilization to remove harmful bacteria from devices for safe use in hospitals and clinics. However, animal experimental evidence shows a link between EtO and increased occurrences of cancer and other adverse events, such as reproductive issues [1–3]. In addition, epidemiologic studies have found that excess cancer mortality occurred among workers exposed to EtO [4, 5].

This research prompted the National Institute for Occupational Safety and Health to recommend that workplaces consider EtO a potential occupational carcinogen and reduce worker exposure appropriately [6]. In 2024, the US Environmental Protection Agency (EPA) published a rule restricting the use of EtO sterilization. With the rule, medical device companies must follow strict regulations to reduce EtO emissions [7].

The new EPA standards have also prompted stakeholders within the medical device and sterilization industries to consider alternative sterilization techniques to EtO. Similarly, the US Food and Drug Administration has encouraged the development of new sterilization methods, such as low-energy radiation, vaporized hydrogen peroxide, nitrogen dioxide, and chlorine dioxide gas [8, 9]. Adopting alternative medical device sterilization techniques at scale requires overcoming many challenges, including establishing the nontoxicity of residuals left on medical devices post-sterilization.

Chlorine dioxide has long demonstrated microbiocidal properties and is highly soluble in water. Unlike chlorine, ClO_2 reaction chemistry does not form chlorinated organic products, such as trihalomethane, which has been tied to an increased risk of cancer [10]. Instead, ClO_2 byproducts

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include chlorite, chlorate, and chloride, which are non-carcinogenic [11]. ClO_2 is not flammable, explosive, carcinogenic, or ozone-depleting at use concentrations [12].

ClO_2 sterilization can be utilized for medical devices, combination products, cold-chain products, and other applications. ClO_2 is injected into a target chamber during sterilization for a fixed time or until a dosage setpoint has been met. Once the exposure is complete, the gas either passes through a carbon scrubber to fully eliminate ClO_2 gas or moves through house exhaust systems and into the outside environment.

To meet regulations, sterilization methods must achieve microbial inactivation to a sterility assurance level of 10^{-6} [13]. ClO_2 is an EPA-registered sterilant capable of inactivating a wide variety of antimicrobial life forms, including bacteria, viruses, algae, fungi, and yeasts. The gas has proven applications for decontaminating isolators, process vessels, ultrafiltration membrane sanitization, water system sanitization, hard surfaces, and cleanrooms [14]. Standard biological indicator testing works for ClO_2 sterilization per the European Committee for Standardization [15].

The International Organization for Standardization (ISO) International Standard 11,135−2014 requires EtO residual levels to meet al.lowable limits specified in ISO 10993-7 [16]. Medical device companies often request residual testing for other gaseous sterilization techniques because of ISO 11,135−2014, even when standards for alternative sterilization techniques do not require residual testing. This introduces a dilemma for ClO_2 because there is no established standard for allowable limits of ClO_2 residuals. In this paper, we introduce novel criteria for defining allowable levels for ClO_2 residuals based on research done by the EPA and the World Health Organization (WHO). We then use these criteria to complete a descriptive analysis of residual levels found on various medical devices post-ClO_2 sterilization.

Table 1 Chlorite and chlorate residual testing acceptance criteria

Drinking water toxicity criteria			
Chemical Tested	Maximum Contaminant Level Goal (mg/L)	Maximum Contaminant Level (mg/L)	
Chlorite	0.8	1.0	
Chlorate	0.7	N/A	
NOAEL/Body weight toxicity criteria			
Chemical Tested	NOAEL (mg/body weight in kg/day)	Average Body Weight (kg)	Maximum Amount (mg/device)
Chlorite	2.9	2.355	6.83
Chlorate	30	2.355	70.65

NOAEL = no-adverse-effect level

2 Materials and Methods

Baron Analytical Laboratories (Connecticut, USA) ran the following tests for medical device manufacturers per its validated ion chromatography process, which can detect chloride, chlorite, and chlorate residual levels down to the parts per million. Ion chromatography is an established and widely used testing method that separates ionized molecules based on differences in charge properties [17, 18]. The amount of water used in ion chromatography testing depends on the minimum amount required to extract the sample and, therefore, varies by the size and shape of each sample. During most procedures, scientists add 10 mL of water until the sample is mostly submerged, then reduce the additions to a few mL at a time until the sample is completely submerged. The water volume is then recorded for each sample.

ClorDiSys (New Jersey, USA) provided all sterilized samples. All samples were sterilized in the Steridox-VP chlorine dioxide sterilizer using an EPA-registered ClO_2 cartridge (EPA label #80802-1).

2.1 Evaluation Criteria for Chlorite and Chlorate Toxicity Levels

Currently, there is no harmonized standard or common specification for ClO_2 residual levels on medical devices. However, toxicity guidelines are in place for the amount of chlorate and chlorite in drinking water (Table 1). According to the EPA, the maximum contaminant level goal for chlorite is 0.8 mg/L, and the maximum containment level for chlorite is 1.0 mg/L [19]. Although chlorate is not included in the EPA guidance, the World Health Organization (WHO) has published a provisional guideline of 0.7 mg/L for chlorate amounts in drinking water [11].

Drinking water guidelines serve as conservative parameters for measuring the toxicity of chlorite and chlorate on devices, since many devices will not be ingested. Additional parameters are needed to determine the allowable amounts of ClO_2 residuals on devices. We developed novel acceptance criteria for ClO_2 residuals using the following approach.

First, we determined the maximum level of byproducts allowed on each device using long-term, oral consumption no-adverse-effect levels (NOAELs). Basing criteria on NOAELs inherently provides a conservative approach to determining the acceptable residual levels for patient-contacting products. Oral limits are standard criteria for evaluating ClO_2 residual testing and have been accepted by regulatory bodies reviewing the data submitted by medical device manufacturers.

According to the EPA toxicology study, the NOAEL for long-term oral consumption of chlorite is 3 mg/kg-day, and the lowest-observed adverse effect level (LOAEL) for long-term oral consumption of chlorite is 14 mg/kg-day [20]. Approximately 400% of the NOAEL can be consumed without crossing the LOAEL. Similarly, the WHO identifies a NOAEL for chlorite of 2.9 mg/kg body weight per day and a NOAEL of 30 mg/kg body weight per day for chlorate [21].

Second, we chose a highly conservative value for patient body weight—the lightest reported anthropometric infant weight. According to the Centers for Disease Control and Prevention (CDC), the 3rd percentile weight (lowest reported) of an infant is 2.355 kg [22].

Finally, we calculated the acceptance criteria for chlorine dioxide residual byproducts on a medical device by multiplying the body weight value and the WHO criteria for the NOAEL of long-term ingestion of these chemicals. Acceptance criteria are listed in Table 1.

Although chloride results are included in the testing, the chloride levels are not included in the toxicity analysis. Chloride ions are abundant elements responsible for ionic homeostasis, osmotic pressure, and acid-base balance in the human body [23]. According to the WHO, chloride concentrations in water exceeding 250 mg/L may affect the taste of the water [24]. Chloride is present in most things and is not considered toxic unless levels in the body are unbalanced. For the typical adult, chloride levels should range between 96 and 106 milliequivalents per liter (approximately 3403.20 mg/L to 3757.70 mg/L) [25].

3 Medical Device Testing

3.1 Medical Device with Incidental Patient Contact

This set of medical devices was pulled from the sterilization chamber directly after the aeration phase to represent the minimum degassing conditions for chlorine dioxide sterilization. The set contained three groups divided into three samples. The first group went through one full ClO_2 sterilization cycle. The second went through two full ClO_2 sterilization cycles, and the third group went through just the second full ClO_2 sterilization cycle. The samples were frozen after aeration.

Baron Laboratories stored the samples in a freezer at −26.1 °C (−15.0 °F) until extraction. Samples were extracted sequentially in 27 mL aliquot of distilled water at 35.5 °C (96 °F) for two hours each. The extraction volume was maintained at 27 mL throughout the procedure by adding 1 mL of distilled water for each 1 mL taken out for injection. A control sample was prepared and extracted under the same conditions as the samples.

3.2 Device to Treat Corneal Abrasions

Residual testing involved three sterilized samples and one control sample of a device to treat corneal abrasions. The spike disks from each of the four devices were placed in separate glass vials filled with 5 mL of deionized water at room temperature for one hour before undergoing analysis.

3.3 Smoking Cessation Inhaler

Residual testing included twelve sterilized samples of a smoking cessation inhaler. Each sample was placed in a 100 mL beaker and then extracted with 37 mL of deionized water at room temperature for one hour.

3.4 Device for Treating Embolisms

Residual testing included four sets of 30 syringes used to treat embolisms. Two sets were filled with 1 mL of deionized water, and two were left empty. One filled set and one empty set were exposed to chlorine dioxide sterilization. All four samples were then sent to the lab for analysis.

The two filled sets of syringes were split into three groups of ten and then composited. Compositing samples boosts the signals of any analytes that may otherwise be undetectable by the testing instrument. An aliquot of the sample from the composite was removed for analysis. The two sets of empty syringes were also split into three groups of ten. Each group was placed in 300 mL of deionized water for one hour at room temperature before testing.

3.5 Polychlorotrifluoroethylene (PCTFE) Bottles

Testing included four sample PCTFE bottles: two large and two small. One bottle of each size was sterilized using ClO_2. The large bottles were submerged in 300 mL of deionized water for one hour at room temperature before testing. Small bottles were submerged in 30 mL of deionized water for one hour at room temperature.

3.6 Syringes Intended for Use with an Ophthalmologic Drug

Samples included 200 syringes: 140 syringes filled with 170 µL of type 1 high-performance liquid chromatography (HPLC) grade distilled water and 60 unfilled syringes. Seventy filled syringes were exposed to ClO_2 sterilization, and 70 were used as controls. Thirty unfilled syringes were exposed to ClO_2 sterilization, and 30 were used as controls.

Filled samples were split into three groups of 23 syringes. Syringe contents of each group were composited into 4 mL glass vials, which scientists then ran in duplicate for the three separate analytes (chlorite, chlorate, chloride). Unfilled samples were split into three groups of 10 syringes. Each group was composited in 250 mL of deionized water for two hours at room temperature. Solutions from each composite were run in duplicate for the three separate analytes.

3.7 Statistical Analysis

Researchers used averages to analyze testing results when samples were tested in duplicate. The averages were calculated by adding the residual levels and dividing the sum by the number of samples. This exploratory study is not powered for formal hypothesis testing and is intended as a descriptive analysis of the results.

4 Results

Results for the medical device with incidental patient contact showed chlorite and chlorate levels were undetectable within the sensitivity of the testing instrument (0.00378 mg/piece and 0.00189 mg/piece, respectively) (Table 2). Similarly, results for the device to treat corneal abrasions showed no detectable concentrations or amounts of chlorite or chlorate in the sterilized samples within the indicated instrument sensitivity (Table 2). Residual levels found on the smoking cessation inhaler are based on the 37 mL extraction volume. On average, no chlorite was detected under the sensitivity of the testing instrument (0.0074 g/piece), which is well within acceptable levels (6.83 g/device). The average chlorate was 0.0157 mg per piece, well under the NOAEL level of 70.65 mg per device (Table 2). For the full results of testing done on the smoking cessation inhaler, see Appendix A.

Residual testing results for the device for treating embolisms are based on calculations from the raw data (Appendix A). To calculate the filled sample summaries, the raw values were averaged, divided by 10 for the number of syringes used in the composite, and then multiplied by the volume of the composite (10 mL). To calculate the unfilled sample summaries, the raw values were averaged, divided by 10 for the number of syringes in each group, and then multiplied by the volume used (300 mL). The final values are given in mg. The average amount of chlorate in the sterilized fluid and sterilized syringe was not detectable under the indicated sensitivity levels for the instrument. The average amount of chlorite was not detectable per instrument sensitivity level in the sterilized syringe and 0.00074 mg/piece in the sterilized fluid (Table 2). This amount is well beneath the NOAEL level of 6.83 mg/device.

Results for ion chromatography tests run on the PCTFE bottles show that no chlorite was detected within instrument sensitivity limits of 0.36 mg/L for the small bottles and 0.75 mg/L for the large bottles (Table 2). Similarly, no chlorate residuals remained on the small bottles under the instrument sensitivity limits. Instrument sensitivity levels for the large bottle tests were 0.05 mg/L above the acceptable chlorite limits, so the measure cannot be used to make a final judgment, although no residuals were found.

Table 2 displays the averages of results from all three composites of each group of syringes intended for use with an ophthalmologic drug. See Appendix A for raw results. Residual levels of chlorite and chlorate in both the ingress and unfilled samples were below the drinking water and NOAEL thresholds.

5 Discussion

Testing results meet either one or both evaluation criteria for residual toxicity (Table 3). The results did not vary between the experimental groups in experiments that tested non-sterilized and sterilized samples. Minimal chlorate levels were found in ophthalmologic drug samples that did not undergo ClO_2 sterilization, indicating that residuals may be present in the natural environment. Also, samples prepared immediately after aeration, without a degassing period, had acceptable levels of residuals.

5.1 Limitations

Although these results represent the range of devices typically used in ClO_2 sterilization, the list is non-exhaustive. Also, for both of the ingress experiments here, the makeup of the solution within the syringe was deionized water and not the drug itself. Future experiments could capture how sterilization impacts drug formulation and residual levels on devices not listed in Table 3, such as implantable devices.

The criteria for chlorite and chlorate levels assume direct contact through oral consumption. They are therefore suitable for medical devices with limited contact with the human body, either in terms of the contact method or the duration of contact. Manufacturers of implantable devices and other long-term, high-contact devices must refer to ISO 10,993 for determining appropriate levels. Future research is necessary to determine residual toxicity criteria for chlorite and chlorate on high-contact devices.

Regulatory bodies currently do not provide limits on chloride residual levels for medical devices. The maximum chloride residual level detected on a device after sterilization in this analysis was 1.03 mg/L, and most levels were below 0 mg/L (Table 2). These results are minuscule when

Table 2 Residual testing results

Device for incidental contact				
	Description	Average Chlorite (mg/piece)	Average Chloride (mg/piece)	Average Chlorate (mg/piece)
Group 1	Post full cycle #1	ND < 0.00378	0.01917	ND < 0.00189
Group 2	Post full cycle #1 and #2	ND < 0.00378	0.01287	ND < 0.00189
Group 3	Post full cycle #2	ND < 0.00378	0.0175	ND < 0.00189
Acceptable Limit		< 6.83 mg/device	N/A	< 70.65 mg/device
Result (Pass/Fail)		***Pass***	***Pass***	***Pass***
Device to treat corneal abrasions				
Concentration (mg/L)				
		Chlorite	Chloride	Chlorate
Control		ND < 0.02	0.13	ND < 0.1
Sterilized Sample 1		ND < 0.02	0.68	ND < 0.1
Sterilized Sample 2		ND < 0.02	1.03	ND < 0.1
Sterilized Sample 3		ND < 0.02	0.34	ND < 0.1
Acceptable Limit		< 0.8 mg/L	N/A	< 0.7 mg/L
Result (Pass/Fail)		***Pass***	***Pass***	***Pass***
Smoking cessation inhaler				
		Average Chlorite (mg/piece)	Average Chloride (mg/piece)	Average Chlorate (mg/piece)
Batch		ND < 0.00074	0.1258	0.0157
Acceptable Limit		< 6.83 mg/device	N/A	< 70.65 mg/device
Result (Pass/Fail)		***Pass***	***Pass***	***Pass***
Device to treat embolism				
		Average Chlorite (mg/piece)	Average Chloride (mg/piece)	Average Chlorate (µg/piece)
Ingress Unsterilized		ND < 0.00003	0.00006	ND < 0.00007
Ingress Sterilized		0.00074	0.00053	ND < 0.00007
Unsterilized		ND < 0.0009	0.0012	ND < 0.0021
Sterilized		ND < 0.0009	0.003	ND < 0.0021
Acceptable Limit		< 6.83 mg/device	N/A	< 70.65 mg/device
Result (Pass/Fail)		***Pass***	***Pass***	***Pass***
Polychlorotrifluoroethylene bottles				
		Chlorite (mg/L)	Chloride (mg/L)	Chlorate (mg/L)
Small Bottle, Unsterilized		ND < 0.36	1.81	ND < 0.36
Small Bottle, Sterilized		ND < 0.36	2.23	ND < 0.36
Small Bottle, Sterilized (Duplicate)		ND < 0.36	3.73	ND < 0.36
Large Bottle, Unsterilized		ND < 0.75	4.31	ND < 0.75
Large Bottle, Sterilized		ND < 0.75	2.59	ND < 0.75
Large Bottle, Sterilized (Duplicate)		ND < 0.75	8.76	ND < 0.75
Acceptable Limit		< 0.8 mg/L	N/A	< 0.7 mg/L
Result (Pass/Fail)		***Pass***	***Pass***	***Non-conclusive***
Prefilled syringes intended for ophthalmologic drug				
		Average Chlorite (mg/L)	Average Chloride (mg/L)	Average Chlorate (mg/L)
Ingress control		ND < 0.14	0.19	0.12
Ingress sterilized		ND < 0.14	0.25	0.18
Control		ND < 0.14	0.17	0.12
Sterilized		ND < 0.14	ND < 0.16	ND < 0.07
Acceptable limit		< 0.8 mg/L	N/A	< 0.7 mg/L
Result (Pass/Fail)		***Pass***	***Pass***	***Pass***

Instrument sensitivity levels were 0.05 mg/L above the acceptance criteria for the large bottles. Although the tests showed no detectable levels of chlorate residuals, the results are considered non-conclusive because of the instrument sensitivity levels.ND < = none detected less than

compared to the minimum amount of chloride recommended for typical adults (approximately 3757.70 mg/L). However, for a comprehensive toxicity assessment, chloride residuals are important to consider, especially in high-contact, long-term devices. Future studies on chlorine dioxide residual toxicity in these types of devices should also include analysis of chloride residual levels.

Since this is a descriptive analysis of chlorine dioxide residual testing ordered from different medical device manufacturers, the results were reported in multiple

Table 3 Testing results summary

Experiment	Device Tested	Residual Levels Meet Evaluation Criteria
1	Device indicated for incidental contact	✓
2	Device for treating corneal abrasions	✓
3	Smoking cessation inhaler	✓
4	Device for treating embolisms	✓
5	Polychlorotrifluoroethylene bottles	✓[a]
6	Syringes for use with an ophthalmologic drug	✓

[a]Results were non-conclusive for the large polychlorotrifluoroethylene bottles due to instrument sensitivity levels. Residual levels from the small polychlorotrifluoroethylene bottles met the evaluation criteria

configurations (mg/L or micrograms/device). Although not ideal, the results can still be evaluated against the toxicity criteria, given that it also has multiple configurations.

Another limitation of this descriptive analysis of third-party testing results is that the authors did not have control over the instrument sensitivity levels. For one test, the sensitivity levels were 0.05 mg/L above the criteria. Even though no residuals were found on the device, the result was deemed inconclusive because of the sensitivity levels. Designing an experiment with instrument sensitivity levels set below the acceptance criteria would ensure all results were conclusive.

The acceptance criteria for chlorite and chlorate residual toxicity were determined independently of the laboratory testing and compared against the results. Testing was ordered and funded by medical device manufacturers and completed by Baron Laboratories. ClorDiSys' involvement in the testing was solely to provide sterilization services to the medical device manufacturers. The device manufacturers reviewed all reports, and the results were independently verified.

6 Conclusion

Under a variety of sterilization situations and devices, ClO_2 residual levels remain well below acceptable limits. These results support the conclusion that ClO_2 sterilization does not leave toxic residuals after application and make a case for several highly conservative methods of measuring residual toxicity as well as what those conservative levels for acceptance should be. ClO_2 sterilization is an effective, certified alternative to EtO sterilization [12, 26]. Results illustrating its nontoxicity post-sterilization further support ClO_2 sterilization adoption in sterilizing medical devices with limited patient contact. Future research on chlorine dioxide residuals must include high-contact medical devices, such as implantable devices, designed for long-term use.

Chlorine dioxide sterilization has additional benefits beyond effectiveness and safety. The method is ideal for cold-chain sterilization, where products must be kept consistently within a certain temperature. ClO_2 is an effective sterilant at ambient temperatures with relatively short cycle times, so temperature-sensitive products need not experience temperatures above acceptable levels. Unlike other newer technologies, chlorine dioxide is compatible with cellulosic materials such as labels, IFUs, and secondary packaging.

ClO_2 sterilization also streamlines operations. The method does not require degassing to remove toxic residuals so that materials can be handled immediately after the cycle. Also, ClO_2 sterilization can be performed in-house, saving manufacturers the step of transporting products to another facility. The sterilization method is compatible with many medical device materials and ideal for prefilled syringes and devices with complex geometries. ClO_2 is also non-toxic, which simplifies waste disposal and management [15]. ClO_2 is an advantageous alternative for medical device manufacturers and contract sterilizers considering moving away from EtO sterilization.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40846-025-00995-8.

Acknowledgements We thank Kevin Ovian and Zachary Pierson-Nieves from Baron Laboratories for their support in preparing this manuscript. They were not compensated for their contributions. We also thank Kirk Livingston of Livingston Communication, Inc., for his assistance in editing the manuscript. Support for his assistance was funded by ClorDiSys Solutions, Inc.

Author Contributions Paul Lorcheim and Emily Lorcheim contributed to material preparation, data collection and analysis, and study conception and design. Tessa Van Ee wrote the first draft of the manuscript, and all authors commented on previous versions and read and approved the final manuscript.

Data Availability The authors confirm that the data supporting the findings of this study are available within the article.

Declarations

Conflicts of interest Paul Lorcheim and Emily Lorcheim are employed by ClorDiSys Solutions, Inc. They did not receive compensation specific to their work on this manuscript. Tessa Van Ee received payment from ClorDiSys Solutions, Inc. for her work drafting and preparing the manuscript for publication.

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