

## **WP# 21 Residual Testing on a Medical Device – Nov 10, 2021**

### **Background**

Residual levels on a Medical Device need to be acceptable for any sterilization method utilized and based on the use of the Medical Device. According to an FDA Executive Summary from the November 6 – 7th, 2019 meeting of the General Hospital and Personal Use Devices Panel of the Medical Devices Advisory Committee titled: Reduction of Ethylene Oxide Sterilization Emissions for Medical Devices and Potential for Utilizing Other Sterilization Modalities, residues formed from the Chlorine Dioxide sterilization process are chlorine dioxide, chlorates, and chlorite. The executive summary elaborates, stating that these residuals all have low toxicity concerns. These low toxicity concerns can be extensively reviewed in a toxicology review authored by the EPA in September, 2000. [EPA/635/R-00/007 Toxicology Review of Chlorine Dioxide and Chlorite (CAS Nos. 10049-04-4 and 7758-19-2)]. Since the use of chlorine dioxide to sterilize medical devices is a fairly new phenomenon, the acceptable levels of chlorine dioxide residue left on medical devices after the sterilization process has never been defined. The following case study was carried out in order to determine how much (if any) chlorine dioxide residue is present subsequent to a chlorine dioxide sterilization cycle.

### **Case Study**

A particular Medical Device Manufacturer utilized this testing and methodology to receive approvals from both the FDA as well as the EU. Their medical devices are indicated for incidental contact with the patient. Therefore, the risk associated with chlorine dioxide residuals on the medical device is considerably low.

The lab that performed the testing was an approved supplier of the Medical Device manufacturer. They used their validated ion chromatography process to measure the residuals on the medical devices. In order to remove the residuals from the medical devices, they submerged the medical devices in a known amount of solution per ISO 11993-7 [ISO 10993-7:2008 Biological evaluation of medical devices Part 7: Ethylene oxide sterilization residuals]. A verification test at their facility proved that almost all of the residue was dissolved by the solution prior to the ion chromatography testing concentrations using [EPA Method 300.0, Determination of Inorganic Anions by Ion Chromatography].

Chlorine dioxide is a gas when above -40°C (-40°F) at sterilization concentrations. Therefore, chlorine dioxide was not expected to reside on the product in its liquid or solid states. The gas rapidly degrades to chlorite when submerged in an aqueous solution. Therefore, no chlorine dioxide was expected to remain as a residual on the product or in solution during the residual testing. Rather, its byproducts were tested for residuals on the product.

Due to the lack of a harmonized standard or common specification for Chlorine Dioxide residual levels on medical devices, the Medical Device manufacturer was required to justify residual

limits of residual chlorine dioxide byproducts on the product. Although the risk assessment above concluded a low toxicity concern (incidental patient contact indication, and relatively low toxicity concerns of chlorine dioxide byproducts), the Medical Device manufacturer decided on using a conservative residual approach.

The Medical Device manufacturer used long term, oral consumption, no observed adverse effect levels (NOAEL) to determine the maximum level of byproducts allowed on each device. This inherently provided a conservative approach to determining the acceptable residual levels for an incidental patient contacting product.

According to the EPA toxicology study [EPA/635/R-00/007 Toxicology Review of Chlorine Dioxide and Chlorite (CAS Nos. 10049-04-4 and 7758-19-2)], the NOAEL (no observed adverse effect level) and LOAEL (lowest observed adverse effect level) of long-term oral consumption chlorite is 3 mg/kg-day and 14 mg/kg-day respectively. This provides evidence that approximately 400% of the NOAEL can be consumed without crossing the LOAEL.

Similarly, the World Health Organization (WHO) identified a NOAEL of chlorite of 2.9 mg/kg body weight per day. This same report also suggests a NOAEL of chlorate of 30 mg/kg body weight per day. [WHO/SDE/WSH/05.08/86 Chlorite and Chlorate in Drinking-water]

The medical device was indicated for general patient use. To further the conservative determination of allowable residuals, the NOAEL for the lightest reported anthropometric infant weight was chosen. According to the CDC, the 3rd percentile weight (lowest reported) of an infant is 2.355kg. [Refer to attachment I below]

The acceptance criteria for chlorine dioxide residual byproducts on the medical device was calculated by multiplying the defined NOAEL of long-term ingestion of these chemicals by the WHO by 2.355 kg (the 3rd percentile weight of an infant). See Table 1 for the derived acceptance criteria.

Chemical Tested	NOAEL (mg/body weight in kg per day) [5.15]	Average Body Weight (kg)	Maximum Amount (mg/device)
Chlorite	2.9	2.355	6.83
Chlorate	30	2.355	70.65
<b>Table 1</b>			

The medical device had a PCB assembly containing batteries. The batteries could provide a charge within the solution that is used to remove the residuals from the medical device. This could have ultimately reduced the effectiveness of the residual testing. To mitigate this potential, the residual testing units were provided without the PCB assembly. This was acceptable because the entire PCB assembly is encapsulated inside of the medical device. Specifically, the PCB assembly is entirely non-patient contacting.

A minimum of (3) product samples per test group were pulled from the sterilization chamber following the aeration phase of the chamber. These samples were labeled with their group number, and their location within the chamber:

- Group 1 – was pulled after the First Full Cycle. Group 3 replaced Group 1 in the next full cycle load. Group 1 was exposed to one full cycle gas exposure and stored frozen for CD/chlorite/chlorate residual testing.
- Group 2 – was pulled after the second full cycle and stored frozen after 2X full cycles of exposure.
- Group 3 – was pulled after the Second Full Cycle and stored frozen after one full cycle of exposure.

A second set with a minimum of (3) product samples per test group were pulled from the sterilization chamber following the chambers aeration phase and an additional 2 hours of a room temperature and atmospheric pressure degassing phase:

- Group 4 – was pulled after the First Full Cycle. Group 6 replaced Group 4 in the second full cycle load. Group 4 was exposed to one full cycle gas exposure and stored frozen (after a 2 hour wait time) for CD/chlorite/chlorate residual testing.
- Group 5 – was pulled after the second full cycle and stored frozen (after a 2 hour wait time) post 2X full cycles of exposure.
- Group 6 – was pulled after the Second Full Cycle and stored frozen (after a 2 hour wait time) post one full cycle of exposure.

A third set with a minimum of (3) product samples per test group was pulled from the sterilization chamber following the chambers aeration phase and an additional 24 hours of a room temperature and atmospheric pressure degassing phase:

- Group 7 – was pulled after the First Full Cycle. Group 9 replaced Group 7 in the second full cycle load. Group 7 was exposed to one full cycle gas exposure and stored frozen (after a 24 hour wait time) for CD/chlorite/chlorate residual testing.
- Group 8 – was pulled after the second full cycle and stored frozen (after a 24 hour wait time) post 2X full cycles of exposure.
- Group 9 – was pulled after the Second Full Cycle and stored frozen (after a 24 hour wait time) post one full cycle of exposure.

Following the third sets declared aeration period (24 hours), the samples were shipped overnight on cold packs or dry ice to the lab.

All residual testing samples (groups 1 through 3) were tested for chlorine dioxide residuals using the lab validated Ion Chromatography method.

- Residuals were to be removed from each device upon exit of cold storage. The medical devices shall not be provided any significant additional aeration period at the test facility.

- This provided an absolute worst-case simulation equivalent to the device getting used on the patient directly after the declared degassing phase.
- Test results were traceable to the group and lot number.

The second set of Residual Samples were retained and stored frozen until the 0-hour degassing phase residual results were reported. If the 0-hour samples did not comply with the acceptance criteria, then the Second Set were to be tested for CD residuals.

Similarly, the third second set of Residual Samples were retained and stored frozen until the 2-hour degassing phase residual results were reported. If the 2-hour samples did not comply with the acceptance criteria, then the Third Set were to be tested for CD residuals.

The final report clearly indicated the required degassing time required for routine production based on the CD Residual results.

### Case Study Testing Procedure

Three samples of sterilized Medical Devices were received and stored in a temperature monitored freezer at -26.1°C (-15.0°F) until extraction. The samples were extracted sequentially in 1-27 ml aliquot of distilled water at 35.5°C (96°F) for 2 hours each. The extraction beaker was covered with a watch glass to prevent evaporation. A Method Blank was prepared and extracted under the same conditions as the samples. Note: 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 2 mg/L (ppm) Standard of chlorite, chloride and chlorate was also prepared. The results are tabulated below.

### Residual Results

Data: 3/1 Full Cycle #1 1X Residuals                      Lot#056-21

Sample	Chlorite (mg/L)	Chloride (mg/L)	Chlorate (mg/L)
Standard	2.15	2.24	2.14
Method Blank	ND<0.14	ND<0.16	ND<0.07
Sample 1 (174556)	ND<0.14	0.74	ND<0.07
Standard	2.18	2.14	1.98
Method Blank	ND<0.14	ND<0.16	ND<0.07
Sample 2 (174556)	ND<0.14	1.64	ND<0.07
Standard	2.3	2.01	1.99
Method Blank	ND<0.14	ND<0.16	ND<0.07
Sample 3 (174556)	ND<0.14	1.88	ND<0.07
Standard	2.1	2.08	2.01

ND< = None detected less than

**Results:** [REDACTED]

Sample	Chlorite	Chloride	Chlorate
Avg. µg per piece	ND<3.78	19.17	ND<1.89
Standard Deviation	N/A	0.28	N/A

2.0 mg/L Standard	Chlorite (mg/L)	Chloride (mg/L)	Chlorate (mg/L)
Avg. from four injections	2.18	2.11	2.03
Standard Deviation	0.07	0.08	0.06

Date Analyzed: [REDACTED]

Analyst: [REDACTED]

EPA Method 300  
[REDACTED]

Data: 3/2 Full Cycle #2 1X Residuals [REDACTED]

Lot#056-21

Sample	Chlorite (mg/L)	Chloride (mg/L)	Chlorate (mg/L)
Standard	2.10	2.05	1.98
Method Blank	ND<0.14	ND<0.16	ND<0.07
Sample 1, (174561)	ND<0.14	0.63	ND<0.07
Sample 1, (174562)	ND<0.14	0.66	ND<0.07
Standard	2.47	2.39	2.04
Method Blank	ND<0.14	ND<0.16	ND<0.07
Sample 2, (174561)	ND<0.14	0.89	ND<0.07
Sample 2, (174562)	ND<0.14	1.10	ND<0.07
Standard	2.08	2.08	2.00
Method Blank	ND<0.14	ND<0.16	ND<0.07
Sample 3, (174561)	ND<0.14	1.34	ND<0.07
Sample 3, (174562)	ND<0.14	2.13	ND<0.07
Standard	2.23	2.08	2.02

ND< = None detected less than

**Results:** [REDACTED]

Sample	Chlorite	Chloride	Chlorate
Avg. µg per piece	ND<3.78	12.87	ND<1.89
Standard Deviation	N/A	0.15	N/A

**Results:**

Sample	Chlorite	Chloride	Chlorate
Avg. µg per piece	ND<3.78	17.5	ND<1.89
Standard Deviation	N/A	0.24	N/A

2.0 mg/L Standard	Chlorite (mg/L)	Chloride (mg/L)	Chlorate (mg/L)
Avg. from four injections	2.22	2.15	2.01
Standard Deviation	0.15	0.15	0.02

Date Analyzed:

Analyst:

EPA Method 300

Quality	Chlorite (mg/L)	Chloride (mg/L)	Chlorate (mg/L)
Method Detection Limit	0.14	0.16	0.07

	MDL (mg/L)	Dilution Factor (mg/L)	Non-Detected Limit (mg/L)
Chlorite	0.14	27	3.78
Chloride	0.16	27	4.32
Chlorate	0.07	27	1.89

### Summary

The (3) lots tested showed no chlorite and chlorate residuals. Chloride was detected at extremely low levels averaging below 13 µg per device.

	Definition per [5.8]	Average Chlorite	Average Chloride	Average Chlorate
Group 1	Post Full Cycle #1 with no degassing phase.	None Detected (< 3.78 µg/device)	19.17 µg/device	None Detected (< 1.89 µg/device)
Group 2	Post Full Cycle #1 AND #2 with no degassing phase.	None Detected (< 3.78 µg/device)	12.87 µg/device	None Detected (< 1.89 µg/device)
Group 3	Post Full Cycle #2 with no degassing phase.	None Detected (< 3.78 µg/device)	17.50 µg/device	None Detected (< 1.89 µg/device)
Acceptable Limit per [5.8]		< 6.83 mg/device	N/A	< 70.65 mg/device
Result (Pass / Fail)		<b>Pass</b>	<b>Pass</b>	<b>Pass</b>

## Attachment I

## Data Table of Infant Weight-for-age Charts

Males, Birth – 36 Months									
Age (in months)	3rd Percentile Weight (kg)	5th Percentile Weight (kg)	10th Percentile Weight (kg)	25th Percentile Weight (kg)	50th Percentile Weight (kg)	75th Percentile Weight (kg)	90th Percentile Weight (kg)	95th Percentile Weight (kg)	97th Percentile Weight (kg)
0	2.355451	2.526904	2.773802	3.150611	3.530203	3.879077	4.172493	4.340293	4.446488
0.5	2.799549	2.964656	3.20951	3.597396	4.003106	4.387423	4.718161	4.91013	5.032625
1.5	3.614688	3.774849	4.020561	4.428873	4.879525	5.327328	5.728153	5.967102	6.121929
2.5	4.342341	4.503255	4.754479	5.183378	5.672889	6.175598	6.638979	6.921119	7.10625
3.5	4.992898	5.157412	5.416803	5.866806	6.391392	6.942217	7.460702	7.781401	7.993878
4.5	5.575169	5.744752	6.013716	6.484969	7.041836	7.635323	8.202193	8.556813	8.793444
5.5	6.096775	6.272175	6.551379	7.043627	7.630425	8.262033	8.871384	9.255615	9.513307
6.5	6.56443	6.745993	7.035656	7.548346	8.162951	8.828786	9.475466	9.885436	10.16135
7.5	6.984123	7.171952	7.472021	8.004399	8.644832	9.34149	10.02101	10.45331	10.74492
8.5	7.361236	7.555287	7.865533	8.416719	9.08112	9.805593	10.51406	10.96574	11.27084
9.5	7.700624	7.900755	8.220839	8.789882	9.4765	10.22612	10.96017	11.42868	11.74538
10.5	8.006677	8.212684	8.542195	9.12811	9.835308	10.60772	11.36445	11.84763	12.17436
11.5	8.283365	8.495	8.833486	9.435279	10.16154	10.95466	11.7316	12.22766	12.56308
12.5	8.534275	8.751264	9.098246	9.714942	10.45885	11.27087	12.06595	12.5734	12.91645
13.5	8.762649	8.984701	9.339688	9.970338	10.73063	11.55996	12.37145	12.88911	13.23893
14.5	8.971407	9.198222	9.560722	10.20442	10.97992	11.82524	12.65175	13.17867	13.53462
15.5	9.16318	9.394454	9.763982	10.41986	11.20956	12.06973	12.91015	13.44564	13.80724
16.5	9.340328	9.575757	9.95184	10.6191	11.42207	12.29617	13.14969	13.69325	14.06019
17.5	9.504964	9.744251	10.12643	10.80433	11.61978	12.50708	13.37311	13.92444	14.29655
18.5	9.658975	9.90183	10.28968	10.97753	11.80478	12.70473	13.5829	14.14187	14.51909
19.5	9.804039	10.05019	10.4433	11.14047	11.97897	12.89117	13.78133	14.34795	14.73034
20.5	9.941645	10.19082	10.58881	11.29477	12.14404	13.06825	13.97042	14.54484	14.93256
21.5	10.07311	10.32507	10.72759	11.44185	12.30154	13.23765	14.15201	14.73448	15.12777
22.5	10.19957	10.4541	10.86084	11.58298	12.45283	13.40086	14.32772	14.91861	15.31777
23.5	10.32206	10.57895	10.98963	11.7193	12.59913	13.5592	14.499	15.09876	15.50418
24.5	10.44144	10.70051	11.1149	11.85182	12.74154	13.71386	14.66716	15.2763	15.68841
25.5	10.55847	10.81958	11.23747	11.98142	12.88102	13.8659	14.83332	15.45242	15.8717
26.5	10.6738	10.93681	11.35806	12.10889	13.01842	14.01623	14.99848	15.62819	16.05514
27.5	10.78798	11.0528	11.47728	12.23491	13.1545	14.16567	15.16351	15.8045	16.23967
28.5	10.90147	11.16803	11.59567	12.36007	13.2899	14.31493	15.32917	15.98214	16.42609
29.5	11.01466	11.28293	11.71368	12.4849	13.42519	14.46462	15.4961	16.16177	16.61508
30.5	11.12787	11.39782	11.8317	12.60983	13.56088	14.61527	15.66485	16.34395	16.8072



<b>31.5</b>	11.24135	11.513	11.95005	12.73523	13.69738	14.76732	15.83588	16.52915	17.00291
<b>32.5</b>	11.3553	11.62869	12.069	12.86144	13.83505	14.92117	16.00958	16.71773	17.2026
<b>33.5</b>	11.46988	11.74508	12.18875	12.9887	13.97418	15.07711	16.18624	16.91	17.40654
<b>34.5</b>	11.58521	11.8623	12.30948	13.11723	14.11503	15.23541	16.36612	17.10619	17.61495
<b>35.5</b>	11.70137	11.98046	12.43132	13.24721	14.2578	15.39628	16.5494	17.30646	17.82797
<b>36</b>	11.75978	12.03991	12.49268	13.31278	14.32994	15.47772	16.64237	17.40816	17.93625

Females, Birth – 36 Months									
Age (in months)	3rd Percentile Weight (kg)	5th Percentile Weight (kg)	10th Percentile Weight (kg)	25th Percentile Weight (kg)	50th Percentile Weight (kg)	75th Percentile Weight (kg)	90th Percentile Weight (kg)	95th Percentile Weight (kg)	97th Percentile Weight (kg)
<b>0</b>	2.414112	2.547905	2.747222	3.064865	3.399186	3.717519	3.992572	4.152637	4.254922
<b>0.5</b>	2.756917	2.894442	3.101767	3.437628	3.797528	4.145594	4.450126	4.628836	4.743582
<b>1.5</b>	3.402293	3.54761	3.770157	4.138994	4.544777	4.946766	5.305632	5.519169	5.657379
<b>2.5</b>	3.997806	4.150639	4.387042	4.78482	5.230584	5.680083	6.087641	6.332837	6.492574
<b>3.5</b>	4.547383	4.707123	4.955926	5.379141	5.859961	6.351512	6.80277	7.076723	7.256166
<b>4.5</b>	5.054539	5.220488	5.480295	5.925888	6.437588	6.966524	7.457119	7.757234	7.95473
<b>5.5</b>	5.5225	5.693974	5.96351	6.428828	6.96785	7.53018	8.056331	8.38033	8.594413
<b>6.5</b>	5.954272	6.130641	6.408775	6.891533	7.454854	8.047178	8.605636	8.951544	9.180938
<b>7.5</b>	6.352668	6.533373	6.819122	7.317373	7.902436	8.521877	9.109878	9.476009	9.719621
<b>8.5</b>	6.720328	6.904886	7.197414	7.709516	8.314178	8.958324	9.573546	9.95848	10.21539
<b>9.5</b>	7.059732	7.247736	7.546342	8.070932	8.693418	9.360271	10.00079	10.40335	10.6728
<b>10.5</b>	7.373212	7.564327	7.868436	8.4044	9.043262	9.731193	10.39545	10.8147	11.09607
<b>11.5</b>	7.662959	7.856916	8.166069	8.712513	9.366594	10.07431	10.76106	11.19625	11.48908
<b>12.5</b>	7.93103	8.127621	8.44146	8.997692	9.666089	10.39258	11.10089	11.55145	11.85539
<b>13.5</b>	8.179356	8.378425	8.696684	9.262185	9.944226	10.68874	11.41792	11.88348	12.19829
<b>14.5</b>	8.409744	8.611186	8.93368	9.508085	10.20329	10.96532	11.71491	12.19522	12.52078
<b>15.5</b>	8.623887	8.827638	9.154251	9.737329	10.44541	11.22463	11.99438	12.48934	12.82561
<b>16.5</b>	8.82337	9.029399	9.360079	9.951715	10.67251	11.46878	12.25862	12.76825	13.11527
<b>17.5</b>	9.009668	9.21798	9.552723	10.1529	10.88639	11.69972	12.50974	13.03415	13.39204
<b>18.5</b>	9.18416	9.394782	9.73363	10.34241	11.08868	11.91921	12.74964	13.28904	13.65799
<b>19.5</b>	9.348127	9.56111	9.90414	10.52167	11.2809	12.12887	12.98004	13.53473	13.91497
<b>20.5</b>	9.50276	9.71817	10.06549	10.69196	11.4644	12.33016	13.2025	13.77284	14.16467
<b>21.5</b>	9.649162	9.867081	10.21882	10.85446	11.64043	12.52439	13.41844	14.00484	14.40858
<b>22.5</b>	9.788355	10.00887	10.36518	11.01027	11.81014	12.71277	13.62911	14.23205	14.64807
<b>23.5</b>	9.921281	10.1445	10.50553	11.16037	11.97454	12.89636	13.83564	14.45561	14.88432
<b>24.5</b>	10.04881	10.27483	10.64076	11.30567	12.13456	13.07613	14.03902	14.67659	15.11839
<b>25.5</b>	10.17173	10.40066	10.77167	11.44697	12.29102	13.25293	14.24017	14.89587	15.35122
<b>26.5</b>	10.29079	10.52274	10.89899	11.58501	12.44469	13.42753	14.43984	15.11428	15.58363
<b>27.5</b>	10.40664	10.64171	11.02338	11.72047	12.59622	13.60059	14.63873	15.33249	15.81632
<b>28.5</b>	10.5199	10.75819	11.14545	11.85392	12.74621	13.77271	14.83743	15.55113	16.0499
<b>29.5</b>	10.63112	10.87273	11.26575	11.98592	12.89517	13.9444	15.03646	15.7707	16.28491



<b>30.5</b>	10.74078	10.98581	11.38474	12.11692	13.04357	14.11611	15.23626	15.99164	16.52176
<b>31.5</b>	10.84935	11.09789	11.50288	12.24735	13.19181	14.28822	15.43719	16.21432	16.76085
<b>32.5</b>	10.95722	11.20934	11.62054	12.37757	13.34023	14.46106	15.63957	16.43904	17.00245
<b>33.5</b>	11.06475	11.32054	11.73806	12.50791	13.48913	14.63491	15.84365	16.66605	17.24681
<b>34.5</b>	11.17225	11.43177	11.85574	12.63865	13.63877	14.80998	16.04963	16.89553	17.49412
<b>35.5</b>	11.28	11.54332	11.97384	12.77001	13.78937	14.98647	16.25767	17.12762	17.7445
<b>36</b>	11.33404	11.59929	12.03312	12.836	13.86507	15.07529	16.3625	17.24469	17.87089

[https://www.cdc.gov/growthcharts/html\\_charts/wtageinf.htm](https://www.cdc.gov/growthcharts/html_charts/wtageinf.htm)