# 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 |

***Table 1***

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 in 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 [redacted] 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:** [redacted]

| 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: [redacted]

Analyst: [redacted]
EPA Method 300
[redacted]

| 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) | ***Pass*** | ***Pass*** | ***Pass*** |
|---|---|---|---|

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 |
| **31.5** | 11.24135 | 11.513 | 11.95005 | 12.73523 | 13.69738 | 14.76732 | 15.83588 | 16.52915 | 17.00291 |
| **32.5** | 11.3553 | 11.62869 | 12.069 | 12.86144 | 13.83505 | 14.92117 | 16.00958 | 16.71773 | 17.2026 |
| **33.5** | 11.46988 | 11.74508 | 12.18875 | 12.9887 | 13.97418 | 15.07711 | 16.18624 | 16.91 | 17.40654 |
| **34.5** | 11.58521 | 11.8623 | 12.30948 | 13.11723 | 14.11503 | 15.23541 | 16.36612 | 17.10619 | 17.61495 |
| **35.5** | 11.70137 | 11.98046 | 12.43132 | 13.24721 | 14.2578 | 15.39628 | 16.5494 | 17.30646 | 17.82797 |
| **36** | 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)** |
| **0** | 2.414112 | 2.547905 | 2.747222 | 3.064865 | 3.399186 | 3.717519 | 3.992572 | 4.152637 | 4.254922 |
| **0.5** | 2.756917 | 2.894442 | 3.101767 | 3.437628 | 3.797528 | 4.145594 | 4.450126 | 4.628836 | 4.743582 |
| **1.5** | 3.402293 | 3.54761 | 3.770157 | 4.138994 | 4.544777 | 4.946766 | 5.305632 | 5.519169 | 5.657379 |
| **2.5** | 3.997806 | 4.150639 | 4.387042 | 4.78482 | 5.230584 | 5.680083 | 6.087641 | 6.332837 | 6.492574 |
| **3.5** | 4.547383 | 4.707123 | 4.955926 | 5.379141 | 5.859961 | 6.351512 | 6.80277 | 7.076723 | 7.256166 |
| **4.5** | 5.054539 | 5.220488 | 5.480295 | 5.925888 | 6.437588 | 6.966524 | 7.457119 | 7.757234 | 7.95473 |
| **5.5** | 5.5225 | 5.693974 | 5.96351 | 6.428828 | 6.96785 | 7.53018 | 8.056331 | 8.38033 | 8.594413 |
| **6.5** | 5.954272 | 6.130641 | 6.408775 | 6.891533 | 7.454854 | 8.047178 | 8.605636 | 8.951544 | 9.180938 |
| **7.5** | 6.352668 | 6.533373 | 6.819122 | 7.317373 | 7.902436 | 8.521877 | 9.109878 | 9.476009 | 9.719621 |
| **8.5** | 6.720328 | 6.904886 | 7.197414 | 7.709516 | 8.314178 | 8.958324 | 9.573546 | 9.95848 | 10.21539 |
| **9.5** | 7.059732 | 7.247736 | 7.546342 | 8.070932 | 8.693418 | 9.360271 | 10.00079 | 10.40335 | 10.6728 |
| **10.5** | 7.373212 | 7.564327 | 7.868436 | 8.4044 | 9.043262 | 9.731193 | 10.39545 | 10.8147 | 11.09607 |
| **11.5** | 7.662959 | 7.856916 | 8.166069 | 8.712513 | 9.366594 | 10.07431 | 10.76106 | 11.19625 | 11.48908 |
| **12.5** | 7.93103 | 8.127621 | 8.44146 | 8.997692 | 9.666089 | 10.39258 | 11.10089 | 11.55145 | 11.85539 |
| **13.5** | 8.179356 | 8.378425 | 8.696684 | 9.262185 | 9.944226 | 10.68874 | 11.41792 | 11.88348 | 12.19829 |
| **14.5** | 8.409744 | 8.611186 | 8.93368 | 9.508085 | 10.20329 | 10.96532 | 11.71491 | 12.19522 | 12.52078 |
| **15.5** | 8.623887 | 8.827638 | 9.154251 | 9.737329 | 10.44541 | 11.22463 | 11.99438 | 12.48934 | 12.82561 |
| **16.5** | 8.82337 | 9.029399 | 9.360079 | 9.951715 | 10.67251 | 11.46878 | 12.25862 | 12.76825 | 13.11527 |
| **17.5** | 9.009668 | 9.21798 | 9.552723 | 10.1529 | 10.88639 | 11.69972 | 12.50974 | 13.03415 | 13.39204 |
| **18.5** | 9.18416 | 9.394782 | 9.73363 | 10.34241 | 11.08868 | 11.91921 | 12.74964 | 13.28904 | 13.65799 |
| **19.5** | 9.348127 | 9.56111 | 9.90414 | 10.52167 | 11.2809 | 12.12887 | 12.98004 | 13.53473 | 13.91497 |
| **20.5** | 9.50276 | 9.71817 | 10.06549 | 10.69196 | 11.4644 | 12.33016 | 13.2025 | 13.77284 | 14.16467 |
| **21.5** | 9.649162 | 9.867081 | 10.21882 | 10.85446 | 11.64043 | 12.52439 | 13.41844 | 14.00484 | 14.40858 |
| **22.5** | 9.788355 | 10.00887 | 10.36518 | 11.01027 | 11.81014 | 12.71277 | 13.62911 | 14.23205 | 14.64807 |
| **23.5** | 9.921281 | 10.1445 | 10.50553 | 11.16037 | 11.97454 | 12.89636 | 13.83564 | 14.45561 | 14.88432 |
| **24.5** | 10.04881 | 10.27483 | 10.64076 | 11.30567 | 12.13456 | 13.07613 | 14.03902 | 14.67659 | 15.11839 |
| **25.5** | 10.17173 | 10.40066 | 10.77167 | 11.44697 | 12.29102 | 13.25293 | 14.24017 | 14.89587 | 15.35122 |
| **26.5** | 10.29079 | 10.52274 | 10.89899 | 11.58501 | 12.44469 | 13.42753 | 14.43984 | 15.11428 | 15.58363 |
| **27.5** | 10.40664 | 10.64171 | 11.02338 | 11.72047 | 12.59622 | 13.60059 | 14.63873 | 15.33249 | 15.81632 |
| **28.5** | 10.5199 | 10.75819 | 11.14545 | 11.85392 | 12.74621 | 13.77271 | 14.83743 | 15.55113 | 16.0499 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **29.5** | 10.63112 | 10.87273 | 11.26575 | 11.98592 | 12.89517 | 13.9444 | 15.03646 | 15.7707 | 16.28491 |
| **30.5** | 10.74078 | 10.98581 | 11.38474 | 12.11692 | 13.04357 | 14.11611 | 15.23626 | 15.99164 | 16.52176 |
| **31.5** | 10.84935 | 11.09789 | 11.50288 | 12.24735 | 13.19181 | 14.28822 | 15.43719 | 16.21432 | 16.76085 |
| **32.5** | 10.95722 | 11.20934 | 11.62054 | 12.37757 | 13.34023 | 14.46106 | 15.63957 | 16.43904 | 17.00245 |
| **33.5** | 11.06475 | 11.32054 | 11.73806 | 12.50791 | 13.48913 | 14.63491 | 15.84365 | 16.66605 | 17.24681 |
| **34.5** | 11.17225 | 11.43177 | 11.85574 | 12.63865 | 13.63877 | 14.80998 | 16.04963 | 16.89553 | 17.49412 |
| **35.5** | 11.28 | 11.54332 | 11.97384 | 12.77001 | 13.78937 | 14.98647 | 16.25767 | 17.12762 | 17.7445 |
| **36** | 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

# Attachment II

## Background Information:

Chlorine dioxide gas is aerated from the chamber at the end of exposure. In a vacuum chamber the gas is removed by pulling vacuum (typically 20KPa), then breaking this with filtered air to bring the pressure up (typically 80KPa), then repeating this cycle a number of times to reduce the CD gas in the chamber to OHSA safe levels of 0.1ppm. CD gas will not exist in the chamber in any measurable amounts. CD gas will have a couple of by-products of its use that will occur on the product, chlorite (ClO2-) and chlorate (ClO3). Chlorite occurs both as a result of being the first reduction product in oxidative reactions in which ClO2 participates. Chlorate on the other hand arises primarily by a disproportionation reaction of ClO2 that is catalyzed by ultraviolet light[i], giving rise to one molecule of ClO2- and one molecule of ClO3- per two molecules of ClO2.[ii]

CSI performed testing on two different material types, 304 stainless steel and ultra-high molecular weight polyethylene (UHMWPE), to determine the amount of residual chlorite left on each surface type after exposure to a chlorine dioxide decontamination cycle. Three identical samples of each material, each with a total surface area of 72 in2 were exposed in a 17 ft3 isolator to the following gassing parameters. First, samples were exposed to 65% relative humidity for a 30-minute condition time, followed by 10.0 mg/L of chlorine dioxide gas for a 1000ppm-hr exposure time (15 minutes). Once the gassing cycle was complete, each sample was placed in a beaker with 200 mL of distilled water for 25 minutes followed by 5 minutes of stirring to dissolve any residual chlorite that may have formed during gassing. The solution was then run through the Hach AutoCAT 9000 Amperometric Titrator to measure the level of residual chlorite. Current EPA regulations allow for approximately 0.007 mg of ClO2-/in2. The highest measured amount of chlorite residual on stainless steel was 0.00041 mg of ClO2-/in2 while the highest amount measured on UHMWPE was 0.00029 mg of ClO2-/in2. Both experimental results are far below their allowable limits.[iii]

Below are some information taken directly from the National Toxicology Program (NTP) and WHO.

NTP Sodium Chlorate 3-WEEK STUDY IN RATS [iv]

> Groups of 10 male and 10 female rats were exposed to drinking water containing 0, 125, 250, 500, 1,000, or 2,000 mg/L sodium chlorate for 3 weeks (equivalent to average daily doses of approximately 20, 35, 75, 170, and 300 mg sodium chlorate/kg body weight per day for males and 20, 40, 75, 150, and 340 mg/kg per day for females). All rats survived to the end of the study. Mean body weights of exposed groups were similar to those of control groups. Water consumption by exposed rats was generally similar to that by control groups throughout the study. An exposure concentration-related decrease in segmented neutrophil counts occurred in male and female rats on days 4 and 22. Heart weights were significantly decreased in 2,000 mg/L males. The incidences of minimal to mild thyroid gland follicular cell hypertrophy were significantly increased in males and females exposed to 500 mg/L or greater.
>
> Sodium Chlorate 3-WEEK STUDY IN MICE
>
> Groups of 10 male and 10 female mice were exposed to drinking water containing 0, 125, 250, 500, 1,000, or 2,000 mg/L sodium chlorate for 3 weeks (equivalent to average daily doses of approximately 20, 45, 90, 175, and 350 mg/kg per day for male mice and 20, 45, 95, 190, and 365 mg/kg per day for female mice). All mice survived to the end of the study. Mean body weights of exposed groups were generally similar to those of control groups. Water consumption by exposed mice was generally similar to that by control groups throughout the study. No exposure-related lesions occurred in male or female mice.
>
> Sodium Chlorate GENETIC TOXICOLOGY
>
> Sodium chlorate was not mutagenic in Salmonella typhimurium strains TA97, TA98, TA100, TA102, TA104, or TA1535; all tests were conducted with and without exogenous metabolic activation (induced rat or hamster liver S9 enzymes). In vivo, no increases in the frequencies of

micronucleated normochromatic erythrocytes were seen in peripheral blood samples from male and female B6C3F1 mice exposed to sodium chlorate in drinking water for 3 weeks.

WHO 3.2 Chlorite and chlorate[v]

3.2.1 Kinetics and metabolism in laboratory animals and humans

Chlorite and chlorate are rapidly absorbed into the plasma and distributed throughout the body, with the highest concentrations in plasma. At typical low drinking-water levels, chlorite would be decomposed by oxidation–reduction reactions with saliva and stomach contents. The rate of reduction of chlorate is slower than that of chlorite, as indicated by its measured biphasic half-lives in the rat of 6 and 36.7 hours, respectively (Abdel-Rahman, Couri & Bull, 1984).

Chlorite and chlorate are excreted primarily in the urine, with lesser amounts excreted in faeces. Most of the chlorine label is in the form of chloride, with lesser amounts of chlorate; chlorite is rarely detected (Abdel-Rahman, Couri & Bull, 1982; Hakk, Smith & Shappell, 2007). Abdel-Rahman, Couri & Jones (1980) and Abdel-Rahman, Couri & Bull (1984) concluded that once chlorite and chlorate are ingested, they are rapidly degraded in the body to chloride and consequently are not considered to be of toxicological concern following chronic exposure in drinking-water.

3.2.2 Effects on laboratory animals and in vitro test systems

The text in this section has been taken primarily from WHO (2008), with some minor editing. The details and references for the studies cited in this section may be found in WHO (2008), which is available online at http://www.inchem.org/documents/jecfa/jecmono/v59je01.pdf. The citation of references in this section indicates that the text has not been taken directly from WHO (2008). The critical studies are identified here and in Section 5. The EFSA (2014) evaluation of perchlorate was also reviewed, and it was concluded that although it utilized a different risk assessment approach, the report included no significant additions to the studies evaluated by WHO (2008).

3.2.2.1 Acute, short-term and long-term exposure

ASC and chlorite are of moderate acute toxicity, but only limited acute toxicity data were available on chlorate. Studies conducted with sodium chlorite in a number of species demonstrated that the most consistent finding is oxidative stress associated with changes in erythrocytes. This observation was also supported by a number of biochemical studies conducted in vitro. Some studies have indicated that the effect may be related to a reduction in serum glutathione levels, thus reducing the body's ability to protect the erythrocytes from the effects of sodium chlorite. Other studies have indicated that sodium chlorite may cause damage to the erythrocyte membrane. For effects on erythrocytes, the lowest lowest-observed-adverse-effect level (LOAEL) of 19 mg/kg bw per day, expressed as chlorite, was derived from a 13-week gavage study in rats in which the NOAEL was 7.4 mg/kg bw per day, expressed as chlorite. Studies on sodium chlorate in a number of species showed some effects on haematological parameters and on body weight gain.

Although sodium chlorate has also been reported to have effects on erythrocytes, changes in thyroid histology (e.g. colloid depletion, hypertrophy, incidence and severity of hyperplasia) and in thyroid hormones were the most sensitive effects observed in rats administered sodium chlorate in drinking-water for 21 or 90 days. Male rats were more sensitive than females, as is commonly seen with substances that affect thyroid function. In one of the two available 90-day studies, thyroid hypertrophy and decreased colloid were observed in male rats given sodium chlorate at drinking-water concentrations of 1 mg/L as chlorate (equivalent to about 0.1 mg/kg bw per day as chlorate) and above. In general, effects including incidence and severity of follicular cell hyperplasia were dose related and more consistently observed at chlorate doses of 75 mg/kg bw per day and above.

3.2.2.2 Carcinogenicity and mutagenicity

Sodium chlorite was not carcinogenic following a number of long-term studies, although these were not conducted to current standards. The International Agency for Research on Cancer

concluded in 1991 that sodium chlorite was not classifiable with respect to carcinogenicity to humans. Sodium chlorite has given positive results in some, but not all, in vitro genotoxicity assays and in one of the two available in vivo mouse micronucleus assays involving intraperitoneal administration. Negative results were obtained in several in vivo assays, for induction of bone marrow micronuclei, chromosome aberrations and sperm head abnormalities, involving oral administration of sodium chlorite to mice.

[i] Stevens, A. A. Reaction products of chlorine dioxide. Environ. Health Perspect. 46: 101-110 (1982).

[ii] Couri, D., Abdel-Rahmant M.S., and Richard J. Bull R.J. Toxicological Effects of Chlorine Dioxide, Chlorite and Chlorate. Environmental Health Perspectives, 46: 13-17 (1982).

[iii] ClorDiSys internal report "Report for Residual Chlorite Materials Testing", Report Number: R-12-0427

[iv] NTP TECHNICAL REPORT ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF SODIUM CHLORATE (CAS NO. 7775-09-9), NATIONAL TOXICOLOGY PROGRAM, December 2005, NTP TR 517, NIH Publication No. 06-4457

[v] WHO/FWC/WSH/16.49 Chlorine Dioxide, Chlorite and Chlorate in Drinking-water, Background document for development of WHO Guidelines for Drinking-water Quality