

## Overview of Chlorine Dioxide (ClO<sub>2</sub>)

The compound chlorine dioxide (ClO<sub>2</sub>), now commercially important, is not in fact a recent discovery. The gas was first produced by Humphrey Davy in 1811 when reacting hydrochloric acid with potassium chlorate. This yielded "euchlorine", as it was then termed. Watt and Burgess, who invented alkaline pulp bleaching in 1834, mentioned euchlorine as a bleaching agent in their first patent. Chlorine dioxide then became well known as a bleach and later a disinfectant. Since the beginning of the twentieth century, when it was first used at a Spa in Ostend, Belgium, ClO<sub>2</sub> has been known as a powerful disinfectant of water. The production of ClO<sub>2</sub> from the chlorate is complicated however, and the gas is explosive, so that it could not be easily utilized practically until the production of sodium chlorite by Olin Corporation in 1940. Chlorine dioxide could now be released when necessary from the chlorite salt. In municipal water supplies this is usually done by adding chlorine to the chlorite solution, and in the laboratory by adding an acid to the chlorite solution. Alliger showed in 1978,<sup>1,2</sup> that ClO<sub>2</sub> could be applied topically by the individual user.

Although ClO<sub>2</sub> is a strong oxidizing agent and a particularly fast disinfectant, there are no reports in the scientific literature of toxicity by skin contact or ingestion, or moreover of mutagenicity. It would seem that effective application of this compound as a topical medication for skin diseases,<sup>3,4</sup> as a disinfectant on food, as well as a cold sterilant on instruments and glassware, is long overdue.

ClO<sub>2</sub> in some respects is chemically similar to chlorine or hypochlorite, the familiar household bleach. However, ClO<sub>2</sub> reactions with other organic molecules are relatively limited as compared to chlorine. When ClO<sub>2</sub> is added to a system – whether a wound or a water supply – more of the biocide is available for disinfection and not consumed by other materials.<sup>5,6</sup> Until 1963 hypochlorite was a standard product of the British Pharmacopoeia (for skin medications), and burn patients even now are bathed in hypochlorite solution at some U.S. burn centers. However, for many reasons ClO<sub>2</sub> makes a likely substitute for the better known hypochlorite since it is far less toxic and irritating when applied to the human body. ClO<sub>2</sub> for example, does not hydrolyze to form HCl as does chlorine, but remains a true gas dissolved in solution. ClO<sub>2</sub>, unlike chlorine or hypochlorite, does not form chlorinated hydrocarbons when in contact with organic matter, or readily add to double bonds. This is a prime concern since many chlorinated hydrocarbons are known to be carcinogenic. Of the amino acids, the building blocks of proteins, only aromatic amino acids and those containing sulfur react with ClO<sub>2</sub>. When hypochlorite is applied to the skin, nitrogen trichloride is formed, a compound which appears in trace quantities but is toxic and irritating. Also, hypochlorite in swimming pool water produces chloramine, an eye irritant, and in wastewater, chloroform. Lastly, unlike hypochlorite or chlorine, ClO<sub>2</sub> can treat water at about 10 ppm with no harmful effects to fish. The LC50 for rainbow trout at 96 hours is 290 ppm.<sup>7</sup> For this reason ClO<sub>2</sub>, rather than chlorine, is favored in commercial aquarium water, especially in mammal tanks.<sup>8</sup>

Residuals of available chlorine in effluents from sewage treatment plants, including the hypochlorite ion and chloramines, adversely influence aquatic life in receiving waters ---

the potential adverse effects both on the public health and on aquatic ecosystems due to increased exposure to chlorinated compounds suggests that the use of chlorine relative to other available techniques for the treatment of sewage and other waste-waters must be reevaluated.<sup>9</sup>

At the time of World War I, when Dakins Solution (0.5% hypochlorite) gained fairly wide acceptance as a wound disinfectant, ClO<sub>2</sub> was not similarly adopted as there was, again, no easy way to produce the gas in small quantities, or to transport it. The application of ClO<sub>2</sub> to the body is still not practiced, nor does it seem particularly obvious that it can be. The gas needs to be released or "activated", normally done with strong acids or chlorine just before use. This process appears somewhat unattractive therefore as a disinfectant in the lab or as a home remedy for the skin. Further, once ClO<sub>2</sub> is activated, shelf life is normally on the order of hours.

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#### DECAY OF CHLORINE DIOXIDE IN FRESHWATER

From: Development and Evaluation of an Ion Chromatographic Method for Measuring Chlorite and Chlorate Anions in Bleached Kraft Mill Effluent, NCASL technical bulletin #673, July 1994, p. 3

However, in dilute solutions, in a closed container and absence of light, ClO<sub>2</sub> can remain stable for long periods. This is especially the case in chilled water.

A new compound, DIOXIDERM (formerly CITRONEX) disinfectant gel, makes novel use of ClO<sub>2</sub> and is available as a "skin cream" in a two-part system.<sup>10</sup> The amount to be applied is mixed just before use, and the chlorine dioxide is released slowly. Because disinfection and lesion response are so rapid, the needed extra step of mixing seems unimportant, especially when treating diseases such as diabetic ulcers or pox lesions. Dual or co-dispensers simplify the application. Similarly, a dual toothpaste and mouthwash, DIOXIBRITE and DIOXIRINSE are now available which kill all bacteria and deodorize the mouth. DIOXIGUARD Liquid for instrument and hospital application as well as general topical use, is a fast acting disinfectant. The shelf life after combining the needed quantity is one day. DIOXIGUARD kills all bacteria, viruses and fungi within one minute, including mycobacteria and amoeba.

#### WIDE USE OF CHLORINE DIOXIDE IN INDUSTRY

Paper mills in the U.S. generate an enormous quantity of  $\text{ClO}_2$ , 500 tons daily for bleaching pulp.<sup>11</sup> Although more expensive than chlorine, it is the bleach material of choice because the basic properties of cellulose are not altered. The textile industry applies  $\text{ClO}_2$  similarly, where prevention of injury to the fibers is important. Both cellulosic and synthetic materials are processed in this way, including cottons, acetates, rayons, polyesters, acrylics and nylons. Cotton is not degraded because the oxidation reaction is highly selective toward lignin and hemicellulose components of the fiber.  $\text{ClO}_2$  does not adversely effect old paper prints or drawings, and will clean ancient documents without injury to fibers.

The first use of chlorine ( $\text{Cl}_2$ ) as a water treatment process in the U.S. occurred in Jersey City in 1908<sup>12</sup>, and of chlorine dioxide, at Niagara Falls in 1944.<sup>13</sup>  $\text{ClO}_2$  now purifies water in over 500 water treatment facilities in the U.S.<sup>14</sup> and many more in Europe. Only chlorine dioxide among the common water treatment disinfectants (ozone, chlorine, chloramine, and chlorine dioxide), produces no signs of malignancy in test animals.<sup>15</sup>  $\text{ClO}_2$  is often applied for water treatment other than disinfection, for example, remedying difficult smell and taste problems. Phenols, in particular, are quickly oxidized, and without odorous chlorophenols often produced by chlorine.  $\text{ClO}_2$  is considered the best additive for oxidizing iron and manganese impurities in drinking water, and for eliminating taste and odor due to algae.<sup>16</sup> It also removes cyanides sulfides, aldehydes and mercaptans.  $\text{ClO}_2$  as used in water disinfection is more sporicidal than  $\text{Cl}_2$ <sup>17,18</sup>, a more powerful inactivator of viruses<sup>19</sup>, and inactivator of cysts.<sup>20</sup> In storm water overflow,  $\text{ClO}_2$  has proved active toward all viruses examined.<sup>21</sup>

Another application of  $\text{ClO}_2$  is in the bleaching of fats and flour.<sup>22</sup>

Extensive experience with chlorine dioxide bleaching of tallow (the fat extracted from meat scraps and dead animals) has shown that this is a safe chemical bleaching process. The chlorine dioxide selectively converts color bodies to lighter colored ones without substantial attack on natural antioxidants in the oil which protect it against aging and rancidity. Tallows bleached with Chlorine dioxide meets the "Refine and Bleach Test", is color stable, and is now in use for the manufacture of the highest-grade toilet soaps.<sup>23</sup>

Many nutrition and toxicology studies have been performed assessing chlorine dioxide's effect on flour. Treatment of flour with 200 ppm, fed to rats, had no effect after several generations.<sup>24,25</sup> Flour treated with up to 500 ppm (5 times the concentration in DioxiCure Gel) fed to puppies had no untoward effect.<sup>26</sup> Thirteen human subjects fed experimentally for six weeks with flour products that were treated with doses up to 400 ppm had no detectable toxic symptoms.<sup>27</sup> Flour bleached with normal dosage is not reduced appreciably in nutritive value.<sup>28</sup> Essential fatty acids are generally not effected, but tocopherol and cystine are oxidized.<sup>29</sup> Reactivities of 21 amino acids with  $\text{ClO}_2$  were evaluated using an iodometric assay, only 6 were found to be reactive at pH 6. They were cysteine, histidine, hydroxyproline, proline, tryptophan and tyrosine.<sup>76</sup>

Several other applications within the food industry have been described. The first reported use of  $\text{ClO}_2$  in the canning industry was by Green Giant at LeSueur, Mn. more than 30 years ago. The objective was to conserve water while at the same time control bacteria.<sup>30</sup> When  $\text{ClO}_2$  rather than chlorine is added to process waters recirculated to clean potatoes, starch by-product, previously extracted for gluing cartons, is upgraded to food grade level and a higher market value. Also, the fresh water need is reduced 25%. In this particular process 10 ppm  $\text{ClO}_2$  is added to the wash water in order to maintain a 1 ppm residual.<sup>31</sup> Chlorine dioxide is excellent as a commercial disinfectant in turkey egg sanitation, and its use does not modify the hatching properties of the fertile eggs.<sup>32</sup> The shelf life of tomatoes can be improved by treatment with  $\text{ClO}_2$ .<sup>33</sup>  $\text{ClO}_2$  also finds application in bleaching cherries and as a teat dip for cows to prevent mastitis. The FDA has recently permitted the use of  $\text{ClO}_2$  for disinfecting chickens, beef and fruits and vegetables.

Masschelein, in his book Chlorine Dioxide, cites the following:

Chlorine dioxide destroys the microorganisms in fish, fruits and vegetables; and the treatment can be carried out without altering the nutritive and organoleptic qualities of the foodstuff. It will take place either by 30-minute immersion in an aqueous solution of 50 to 1,000 mg/l (50 to 1000ppm) of  $\text{ClO}_2$  or by exposure to air containing 2,000 to 3,000 ppm of  $\text{ClO}_2$ . This is a very favorable treatment for the storage of frozen foods. Natural foods such as pepper may be sterilized by a treatment with air containing 1,000 to 20,000 ppm of  $\text{ClO}_2$ . The preservation of melted cheese is facilitated by the addition of 100 to 300 mg/l of  $\text{ClO}_2$  to the milk used for its manufacture, and 100 to 400 mg/l to its washing water. The bleaching of oils and greases, particularly those used for alimentary needs, is carried out by a maximum injection of 20,000 mg/l of  $\text{ClO}_2$ . The medicinal odor of cleaning shrimps is eliminated by adding 40 mg/l to the washing water. A dose of less than 100 mg/l of  $\text{ClO}_2$  does not seem to hinder the taste or nutritive value.<sup>34</sup>

The remaining or residual products on fruits and vegetables after treatment with  $\text{ClO}_2$  are apparently chloride and a trace amount of chlorite.<sup>35</sup> A recent patent by Frontier Pharmaceutical involves the lowering of the chlorite residual, and describes a method for the release of  $\text{ClO}_2$  at higher, more physiological pH.

Some industrial applications of  $\text{ClO}_2$  other than bleaching or disinfecting include: the treatment of leather, where  $\text{ClO}_2$  oxidizes disulfide bridges of keratin; stabilization of vinyl and latex enamels; additive in air pollution control for complexing impurities such as mercaptans and aldehydes; controlling odors of fishmeal and rendering plant water effluents; an oxidant in the preparation of vaccines<sup>36,37</sup> and neutralizing toxins<sup>38</sup>; and a copper etchant in the manufacture of electronic component parts.

## DIFFERENCES WITH OTHER OXIDANTS

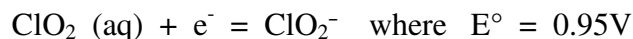
Although chlorine and chlorine dioxide are both strong oxidizing agents, they differ in reactions with various organic and inorganic compounds.  $\text{ClO}_2$  for example, does not combine with ammonia as does  $\text{Cl}_2$ . Chlorine dioxide is a better disinfectant in the presence of organic matter, and bacterial kill is not appreciably changed with change in pH. Hypochlorite has a higher oxidation potential and is an indiscriminate "chlorinator", adding a permanent chlorine atom to organic molecules. This unfortunately, produces a number of unwanted chlorinated hydrocarbons such as chloroform and chlorophenol. Chemicals found in industrial waste discharges for example, all react to produce chlorinated by-products that are hazardous to health.<sup>39</sup>  $\text{ClO}_2$ , on the other hand, oxidizes (removes electrons) without adding an atom of its own to the oxidized product. The pKa for the chlorite ion, chlorous acid equilibrium, is extremely low at pH 1.8. This is different from the hypochlorous acid/hypochlorite base ion pair equilibrium found near neutrality, and indicates the chlorite ion will exist as the dominant species in drinking water and in the human body.

When purifying water supplies,  $\text{ClO}_2$  combines with phenols particularly fast by attacking the benzene ring. Odorless, tasteless products are formed directly, without intermediate compounds, as is the case with chlorine.<sup>40</sup>  $\text{ClO}_2$  may be more effective than copper sulfate in controlling algae; it is believed to attack the pyrrole ring of the chlorophyll which cleaves the ring and leaves the chlorophyll inactive. The reaction of  $\text{ClO}_2$  with algae, again, forms tasteless, odorless products.

Olefins react much more rapidly with permanganate than with chlorine dioxide, whereas, triethylamine is thousands of times more reactive with chlorine dioxide than with permanganate.

Unlike most other oxidizing compounds,  $\text{ClO}_2$ , and its reduction product  $\text{ClO}_2^-$ , can act either as oxidizing or reducing agents (NCASI No. 673). Under acid conditions hydrogen peroxide will reduce  $\text{ClO}_2$  to form chlorous acid, but  $\text{ClO}_2$  also can be oxidized by chlorine to produce chlorate, and by ozone to produce  $\text{Cl}_2\text{O}_6$ .  $\text{ClO}_2^-$  similarly can oxidize iodide to form iodine, or be oxidized by hypochlorite ion to form chlorate. Combining  $\text{ClO}_2$  with blood causes methemoglobin by oxidizing  $\text{Fe}^3$  to  $\text{Fe}^2$  in the red blood cell. Breathing  $\text{ClO}_2$  can have this effect.

When  $\text{ClO}_2$  oxidizes organics, it usually takes in one electron and reduces to  $\text{ClO}_2^-$ .  $\text{ClO}_2$  can oxidize some inorganics, like ferric oxide, remove 5 electrons rather than one, and reduce all the way to chloride. The amount of electron exchange is the oxidizing capacity, not the redox potential or driving force of the reaction.

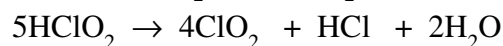
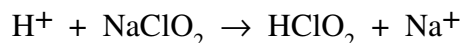


When oxidizing organic molecules, there is no chlorine atom exchange to produce chlorinated hydrocarbons.

## CHEMICAL REACTIONS<sup>41,42,43,44</sup>

### Preparation of $\text{ClO}_2$

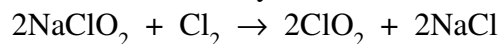
1. Acidification of chlorite



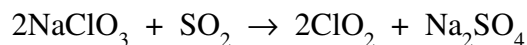
2. Oxidation of chlorite by hypochlorite - for alkaline bleaching & water treatment



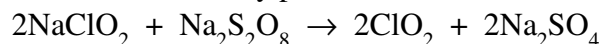
3. Oxidation of chlorite by chlorine



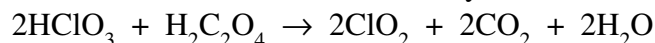
4. Reduction of chlorate with sulfur dioxide - used in pulp bleaching



5. Oxidation of chlorite by persulfate



6. Reduction & acidification of chlorate by oxalic acid



To inhibit further oxidation, the following are good scavengers of  $\text{ClO}_2$ : sulfamic acid, sulfur dioxide, resorcinol, hydroquinone, sodium thiosulfate, sodium bisulfite, sodium sulfite, sodium arsenite and plumbous oxide. Agents that reduce  $\text{ClO}_2$  completely to the chloride ion: borohydride, iodide at pH 1, sulfurous acid, ferrous chloride manganese and vitamin C. Ferrous chloride will eliminate chlorate.

{GRAPH NOT SHOWN}

UV-Vis absorption spectra showing the release of  $\text{ClO}_2$  from sodium chlorite at various pH values. Readings were taken after 60 minutes at ambient temperature. The initial chlorite concentration was 112 ppm. Notice the loss of chlorite at 262 nm as the pH is lowered, with the gain of  $\text{ClO}_2$  at 360 nm. There is little or no release of  $\text{ClO}_2$  above pH 3.<sup>45</sup>

Inorganic Reactions:

- For iodometric analysis  

$$2\text{ClO}_2 + 2\text{I}^- \rightarrow 2\text{ClO}_2^- + \text{I}_2$$
- Oxidation of iron  

$$\text{ClO}_2 + \text{FeO} + \text{NaOH} + \text{H}_2\text{O} \rightarrow \text{Fe}(\text{OH})_3 + \text{NaClO}_2$$
- Oxidation of manganese  

$$2\text{ClO}_2 + \text{MnSO}_4 + 4\text{NaOH} \rightarrow \text{MnO}_2 + 2\text{NaClO}_2 + \text{Na}_2\text{SO}_4 + 2\text{H}_2\text{O}$$
- Oxidation of sodium sulfide  

$$2\text{ClO}_2 + 2\text{Na}_2\text{S} \rightarrow 2\text{NaCl} + \text{Na}_2\text{SO}_4 + \text{S}$$
- Oxidation of nitrogen oxide pollutant  

$$2\text{NO} + \text{ClO}_2 + \text{H}_2\text{O} \rightarrow \text{NO}_2 + \text{HNO}_3 + \text{HCl}$$
- Gas phase reaction with flourine  

$$\text{F}_2 + 2\text{ClO}_2 \rightarrow 2\text{FClO}_2$$
- In alkaline solution  

$$2\text{ClO}_2 + 2\text{OH}^- \rightarrow \text{ClO}_2^- + \text{ClO}_3^- + \text{H}_2\text{O}$$
- Aluminum, magnesium, zinc & cadmium react with  $\text{ClO}_2$   

$$\text{M} + x\text{ClO}_2 \rightarrow \text{M}(\text{ClO}_2)_x$$
- Disproportionation of chlorite depends upon chlorides present, pH, and ratio of ingredients  

$$4\text{ClO}_2^- + 4\text{H}^+ \rightarrow \text{Cl}^- + 2\text{ClO}_2 + \text{ClO}_3^- + 2\text{H}^+ + \text{H}_2\text{O}$$

$$5\text{ClO}_2^- + 4\text{H}^+ \rightarrow 4\text{ClO}_2 + \text{Cl}^- + 2\text{H}_2\text{O}$$
- With hydrogen peroxide as a reducing agent in commercial production of chlorite  

$$2\text{ClO}_2 + \text{H}_2\text{O}_2 + 2\text{NaOH} \rightarrow 2\text{NaClO}_2 + 2\text{H}_2\text{O} + \text{O}_2$$
- A highly colored complex is formed when  $\text{ClO}_2$  is dissolved in an aqueous solution of barium chlorite  $\text{ClO}_2 + \text{ClO}_2^- \rightleftharpoons \text{Cl}_2\text{O}_4$

### Organic Reactions:

- With organic compounds in water  $\rightarrow$  aldehydes, carboxylic acids, ketones & quinones
- With olefins  $\rightarrow$  aldehydes, epoxides, chlorohydrins, dichloro-derivatives, and chloro-and unsaturated ketones.
- With ethylenic double bonds  $\rightarrow$  ketones, epoxides, alcohols
- With benzene  $\rightarrow$  no reaction
- With toluene  $\rightarrow$   $\text{CH}_3$ ,  $\text{CH}_2\text{Cl}$ ,  $\text{CH}_2\text{OH}$
- With anthracene  $45^\circ$   $\rightarrow$  anthraquinone, 1, 4-dichloroanthracene
- With phenanthrene  $\rightarrow$  diphenic acid, 9-chlorophenanthrene
- With 3, 4-benzopyrene  $\rightarrow$  quinones, traces of chlorinated benzopyrene  
(no longer considered carcinogenic)
- With carboxylic and sulfonic functions  $\rightarrow$  no reaction
- With aldehydes  $\rightarrow$  carboxylic acids

11. With ketones → alcohols
12. With aliphatic amines     primary     → slow or no reaction  
                                  secondary  → slow or no reaction  
                                  tertiary    → rupture of CN bond, no N-oxides formed
13. With triethylamine  
$$\text{H}_2\text{O} + (\text{C}_2\text{H}_5)_3\text{N} + 2\text{ClO}_2 \rightarrow (\text{C}_2\text{H}_5)_2\text{NH} + 2\text{ClO}_2^- + \text{CH}_3\text{CHO} + 2\text{H}^+$$
14. With phenol → P-benzoquinone, 2 chlorobenzoquinone
15. Excess  $\text{ClO}_2$  with phenol → maleic acid, oxalic acid
16. With thiophenols → sulfonic acids
17. With tocopherol → demethylated derivatives
18. With saturated acids → no reaction
19. With anhydrides → no reaction but catalyzes hydrolysis
20. With amino acids: glycine, leucine, serine, alanine, phenylalanine, valine, hydroxyproline, phenylaminoacetec, aspartic, glutamic acids → little, or no reaction
21. With amino acids containing sulfur → reactive
22. With methionine → sulfoxide → sulfone
23. With aromatic amino acids → reactive
24. With tyrosine → dopaquinone, dopachrome
25. With tryptophan → idoxyl, isatine, indigo red, trace chlorinated products
26. With thiamine → slow reaction
27. With keratin → hydrosoluble acids
28. With carbohydrates CHO and  $\text{CH}_2\text{OH}$  → carboxylic functions
29. With vanillin pH4 → monomethyl ester, β-formylmuconic acid
30. With pectic acid → mucic acid, tartaric acid, galacturonic acid
31. With chlorophyll and plant dyes → color removed.
32. With latex and vinyl enamels → delays polymerization
33. With naphthaline → no reaction
34. With ethanol → no reaction
35. With biacetyl → acetic acid, carbon dioxide
36. With 2,3-butaneodiol → acetic acid, carbon dioxide
37. With cyclohexene → aldehydes, carboxylic acids, epoxides, alcohols, halides, dienes, ketones
38. With maleic acid → no reaction
39. With fumaric acid → no reaction
40. With crotonic acid → no reaction
41. With cyanides → oxidized
42. With nitrites → oxidized
43. With sulfides → oxidized

Hydrocarbons of longer chain length than  $\text{C}_8$  are the most oxidizable by  $\text{ClO}_2$ .<sup>46</sup>

The organic compounds most reactive with  $\text{ClO}_2$  are tertiary amines and phenols.



Unsaturated fatty acids and their esters are generally oxidized at the double bond.

### $\text{ClO}_2$ DOES *NOT* REACT WITH:

hippuric acid, cinnamic acid, betaine, creatine, alanine, phenylalanine, valine, leucine, asparaginic acid, asparagine, glutaminic acid, serine, hydroxyproline, taurine, aliphatically combined  $\text{NH}_2$  groups, amido and imido groups, HO groups in alcohols and HO acids, free or esterified  $\text{CO}_2\text{H}$  groups in mono and polybasic acids, nitrile groups, the  $\text{CH}_2$  groups in homologous series, ring systems such as  $\text{C}_6\text{H}_6$ ,  $\text{C}_{10}\text{H}_8$ , cyclohexane, and the salts of  $\text{C}_5\text{H}_5\text{N}$ , quinoline and piperidine.

Most aliphatic and aromatic hydrocarbons do not react with  $\text{ClO}_2$  under normal water treatment conditions, unless they contain specific reactive groups. Alcohols are resistant at neutral pH, but under conditions of very low pH, high temperatures or high concentrations, alcohols can react to produce their corresponding aldehydes or carboxylic acids.<sup>47</sup>  $\text{ClO}_2^-$ , chlorite, the reduction product of  $\text{ClO}_2$ , although a less powerful oxidant, is used to react with many malodorous and highly toxic compounds such as unsaturated aldehydes, mercaptans, thioethers, hydrogen sulfide, cyanide and nitrogen dioxide.

**{GRAPH NOT SHOWN}**

UV-Vis absorption spectra<sup>43</sup> for:

- a commercial “stabilized chlorine dioxide oral rinse” at a concentration of 100 ppm chlorite at pH 6.5 (there is no release of chlorine dioxide shown at 360 nm)
- a solution of sodium chlorite ( $\text{ClO}_2^-$ ) at 900 ppm in a phosphate buffer at pH 7
- a sodium chlorate ( $\text{ClO}_3^-$ ), at 900 ppm in a phosphate buffer at pH 7

**{GRAPH NOT SHOWN}**

Uv-Vis spectra of commercially available RetarDex® oral rinse utilizing “stabilized chlorine dioxide” at pH 6.5, 5.15, and 2.2. No  $\text{ClO}_2$  is evolved above pH 5 as shown at 360 nm.<sup>43</sup>

## DIOXIDERM AND DIOXIGUARD EXPERIMENTAL DISINFECTANTS

Studies have shown DIOXIGUARD and DIOXIDERM, which are  $\text{ClO}_2$  or  $\text{ClO}_2$  complexes, to be two of the fastest disinfectants.<sup>48</sup> Bacteria, viruses and even fungi are killed in under 1 minute. This rate of deactivation includes mycobacteria, amoeba and spores (non dried). Two questions immediately come to mind: How does DIOXICURE and DIOXIGUARD work? And, why are they not toxic?

The method of chlorine dioxide bacterial kill at low ppm concentration seems to occur by the disruption of protein synthesis and enzyme inactivation.<sup>49 50</sup> This is similar to the "time honored", non-toxic mechanism of some common antibiotics. Oxidation of RNA and DNA do not appear to take place, or are at least unimportant in the process. The site of action lies in the soluble fraction of the cell; there appears to be no damage to whole structural components such as ribosomes.<sup>51</sup> Bringmann prepared electron micrographs of chlorine-treated cells immediately after contact and observed no visual change in the cells, comparable to those killed with bromine and iodine.<sup>52</sup>

At high  $\text{ClO}_2$  ppm, the method of rapid bacterial and viral kill appears to be the softening and destroying of the cell wall or viral envelope.<sup>53</sup> Human cells do not have cell walls and are apparently unaffected. Our skin and bodies are likely protected from the general oxidative effects of  $\text{ClO}_2$  by the many reducing agents in our cells and blood such as catalase, glutathione, superoxide dismutase, vitamins E, C, A, B complex, uric acid, zinc and selenium. This is probably the same internal protective mechanism that prevents damage from oxygen and free radicals. Bacteria and viruses do not contain most of these reducing compounds.

Because  $\text{ClO}_2$  is a strong oxidizing agent and also itself a free radical, it quickly neutralizes reactive molecules, and oxygen free-radicals that are produced in the body by macrophages such as,  $\text{NO}^\bullet$ ,  $\text{O}_2^-$ ,  $\text{H}_2\text{O}_2$ ,  $\text{HClO}$ , and  $\text{OH}^\bullet$ . These oxygen compounds are released in response to stress or infection and cause inflammation and pain. Other potential irritants found in wounds are similarly oxidized or reduced, such as leukotrienes, TNF, and interleukin. This neutralizing property of  $\text{ClO}_2$ , combined with its ability to completely disinfect, makes DIOXIDERM and DIOXIGUARD ideal wound medications. Unlike iodine compounds, healing is not impeded.<sup>54</sup> Veterinarians have been treating deep wounds and abscesses on tigers and elephants as well as dogs and cats with outstanding success.<sup>56</sup> DIOXIDERM GEL had similar striking results on human (otherwise non-healing) diabetic ulcers.<sup>57</sup> If our body could manage to manufacture chlorine dioxide, as it does hypochlorite, hydrogen peroxide and superoxide, it would certainly do so.

$\text{ClO}_2$  is both a small molecule relative to common organic disinfectants and soluble. It is also a gas and non-ionic. These properties no doubt facilitate the transporting process through the skin or bacterial cell wall.

It is interesting to speculate on the formation of a  $\text{ClO}_2$  complex that may be involved in the disinfection process. Electron configuration of the  $\text{ClO}_2$  molecule theoretically allows combination.  $\text{ClO}_2$  will hydrate for example with water, and also can form compounds with the chlorite ion  $[\text{ClO}_2 \cdot \text{ClO}_2^-]^-$ .<sup>58</sup> A highly colored complex,  $\text{C}_2\text{O}_4^-$ , is formed when  $\text{ClO}_2$  is dissolved in a solution of barium chlorite. There is evidence that more than one oxidant in a disinfectant formula will act synergistically in deactivating microorganisms,<sup>59</sup> for example chlorous acid and chlorine dioxide.

As with household bleach, where hypochlorous acid and not chlorine is the active bacteria killer, it may similarly be chlorous acid although quite unstable, and not chlorine dioxide, which is the more active of the two species. Chlorous acid has a higher oxidation/reduction potential than either  $\text{ClO}_2$  or hypochlorous acid. In Frontier's particular case, DIOXIDERM GEL maintains the chlorous acid concentration since the unstable chlorous acid molecules formed when mixing A & B are far less mobile within a viscous gel matrix. The chlorous molecules can not as easily combine and evolve chlorine dioxide as would be the case in a liquid. The increase in chlorous acid may be the reason that the gel form is the faster disinfectant on wounds and burns. The chemical literature shows that a chlorite/acid mixture producing  $\text{ClO}_2$  has many more times the oxidation power than  $\text{ClO}_2$  alone at similar pH.<sup>60</sup> Interesting too, that the type of acid activator producing the chlorous acid molecule can have an effect on the oxidizing strength of  $\text{ClO}_2$ , or  $\text{ClO}_2$  mixture.<sup>61</sup>

{GRAPH NOT SHOWN}

Comparison of the Disinfection Efficiencies of  $\text{ClO}_2$  with  $\text{Cl}_2$  at pHs of 6.5 and 8.5<sup>62</sup>

Comparison of the Dosage Required to Achieve a 5-Log Reduction in Viable Bacteria at 60-Second Contact Time<sup>63</sup>

## NON-TOXICITY

Many evaluations have shown  $\text{ClO}_2$  compounds to be non-toxic. Five decades of use have not indicated any adverse effects on health. The main areas of use have been disinfecting water supplies, the elimination of unwanted tastes and odors, and bleaching in the pulp and paper and textile industries. Toxicology tests include ingestion of  $\text{ClO}_2$  in drinking water, additions to tissue culture, injections into the blood, seed disinfection<sup>64,65</sup>, insect egg disinfection, injections under the skin of animals and into the brains of mice, burns administered to over 1500 rats, and injections into the stalks of plants. "Standard" tests include, Ames Mutation, Chinese Hamster, Rabbits Eye, Skin Abrasion, Pharmacodynamics and Teratology.<sup>66</sup> In one tissue culture study, highly diluted DioxiDerm liquid was placed on CD4 cells infected with H.I.V.<sup>67</sup> Viruses were inactivated inside the cell, as well as in the supernatant, and with

little damage to the CD4 cell itself. Daughter cells 6 days later, although not as viable as the controls, were not infected. This is particularly impressive considering that most virucides are cytotoxic, even at high dilutions. Similar efficacy and non toxicity was demonstrated on infected cabbage seeds. 4000 seeds heavily infected with bacteria were soaked for about ½ hour in ClO<sub>2</sub> disinfectant. No bacteria remained after this period, and the seeds then grew normally.<sup>68</sup> In order to reduce air and water pollution the EPA is proposing to substitute chlorine dioxide for the usual chlorine bleach in all pulp and paper mills throughout the country. This effects 350 installations and costs the industry about \$4 billion.<sup>69</sup> With a prospect of changing from chlorine to chlorine dioxide in our water supply, the EPA and American Water Works in the past have commissioned over 100 papers and studies on the toxicity of ClO<sub>2</sub>. Many controlled animal studies on the effects of ingesting sodium chlorite and chlorine dioxide have been conducted from 1 to 1000 mg/L concentrations. Metabolically, both ClO<sub>2</sub> and ClO<sub>2</sub><sup>-</sup> are rapidly reduced following ingestion. Radioactive chlorine tests show that most of the tagged chlorine is excreted from the urine in the form of Cl<sup>-</sup> ion with a small amount of ClO<sub>2</sub><sup>-</sup>. The no observed effect level, NOEL, from animal ingestion studies involving ClO<sub>2</sub> and ClO<sub>2</sub><sup>-</sup>, ranges to 100 ppm<sup>70,71,72</sup>, about the concentration of Frontier's DioxiDerm gel for topical use. The half life for the elimination of ClO<sub>2</sub> and ClO<sub>2</sub><sup>-</sup> from the plasma is less than half that of HOCl, hypochlorite.<sup>73</sup>

In one study, human volunteers drank ClO<sub>2</sub> or ClO<sub>2</sub><sup>-</sup> in solution up to 24 ppm and showed no adverse effects.<sup>74</sup> Several studies examined the effects on reproductive toxicity or teratology. There is no evidence of fetal malformation or birth defects at ClO<sub>2</sub> concentrations, in drinking as well as skin route, up to 100 ppm.<sup>75 76 77</sup> With prolonged feeding toxicity is produced mainly in the red blood cell. Rats fed up to 1000 mg/l chronically for 6 months showed no significant hematological changes. After 9 months, however, red blood cell counts, hematocrit and hemoglobin were decreased in all treatment groups.

Lack of toxicity on a long term, but low level basis is dramatically illustrated by two separate studies where rats,<sup>78</sup> and honeybees,<sup>79</sup> were fed ClO<sub>2</sub> in high doses over a two year period. No ill effects were noted with up to 100 ppm added to water supply.

In a skin sensitization study, ClO<sub>2</sub> liquid and gel (similar to DIOXIDERM ) were injected intradermally into guinea pigs, 10 times in about 3 weeks.<sup>80</sup> No sensitivity reaction was observed. At the site of continuous liquid injection, necrotic areas developed due to the low pH of 2.7. This damage was reversible. The pH of Frontier's DIOXIDERM GEL and DIOXIDERM Liquid, however, is much higher at pH 4, and would probably avoid this temporary damage. An ocular irritation study in rabbits indicated redness in the conjunctivae after one hour, which became normal after 24 hours. The cornea and iris remained unchanged after treatment.

Fast disinfection and non-toxicity are properties normally not found side-by-side in the same compound. For example, formaldehyde and peracetic acid are strong and often used sterilants, but they are also toxic and irritating. Because both speeds of deactivation and non-toxicity are combined in DIOXIDERM biocides, new possibilities are opened for important skin products, as well as commercial surface disinfection.

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