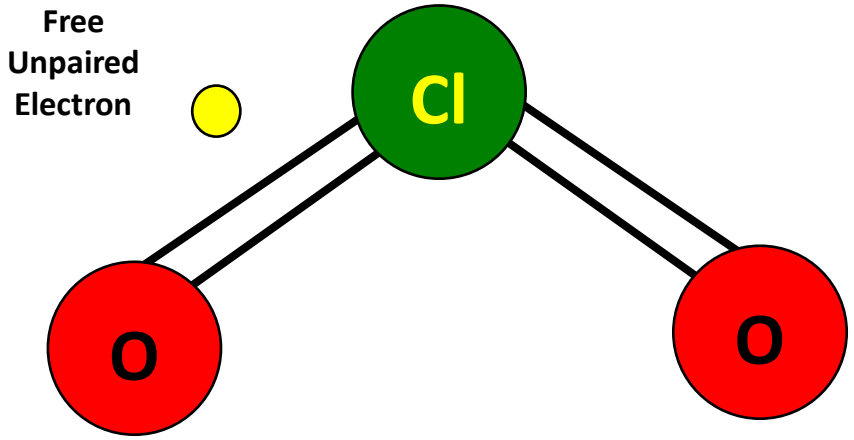
Overall View of ClO_2

By Howard Alliger



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Overall View of ClO_2

The compound chlorine dioxide (ClO_2), 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_2 has been known as a powerful disinfectant of water. The production of ClO_2 from the mineral, chlorate, is complicated however, and the gas is explosive, so that it could not be easily utilized practically until the production of sodium chlorite powder 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,[1,2] that ClO_2 could be applied topically by the individual user.

Although ClO_2 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,[3,4] as a disinfectant on food, as well as a cold sterilant on instruments and glassware, is long overdue.

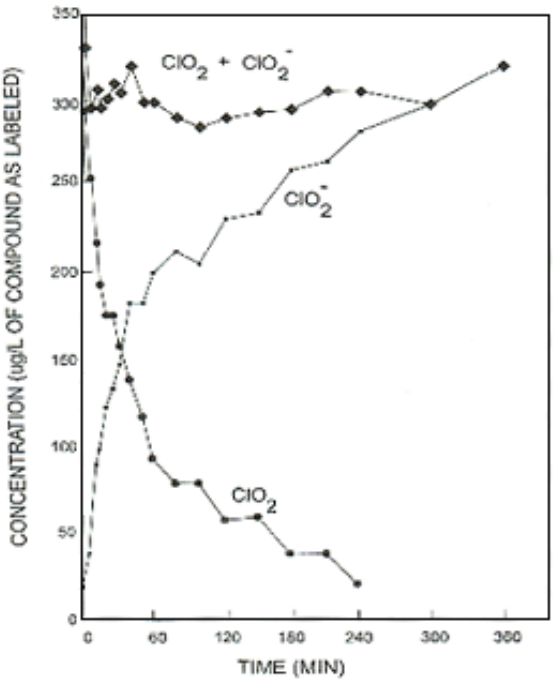
ClO_2 in some respects is chemically similar to chlorine or hypochlorite, the familiar household bleach. However, ClO_2 reactions with other organic molecules are relatively limited as compared to chlorine. When ClO_2 is added to a system – whether a wound or a water supply – more of the biocide is available for disinfection and not consumed by other materials.[5,6] 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_2 makes a likely substitute for the better known hypochlorite since it is far less toxic and irritating when applied to the human body and wounds.

ClO_2 does not hydrolyze to form HCl as does chlorine, but remains a true gas dissolved in solution. ClO_2, 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_2. 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_2 can treat water at about 10 ppm with no harmful effects to fish. The LC50 for rainbow trout at 96 hours is 290 ppm.[7] For this reason ClO_2, rather than chlorine, is favored in commercial aquarium water, especially in mammal tanks.[8]

> 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.[9]

At the time of World War I, when Dakins Solution (0.5% hypochlorite) gained fairly wide acceptance as a wound disinfectant, ClO_2 was not similarly adopted as there was no easy way to produce the gas in small quantities, or to transport it. The application of ClO_2 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_2 is activated, shelf life is normally on the order of an hour.

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 glass container and absence of light, ClO_2 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_2 and is available as a "skin cream" in a two-part system.[10] The amount to be applied is mixed just before use automatically, and the chlorine dioxide is released slowly. Lesion response is rapid, especially when treating diseases such as pox lesions or acne. Dual dispensers simplify the application. Similarly, a new dual toothpaste and mouthwash, DIOXIBRITE and DIOXIRINSE are now available which kill all bacteria in vitro and deodorize the oral cavity. DIOXIGUARD Liquid for instrument and hospital application as well as general topical use, is a fast acting disinfectant, and kills all bacteria, viruses and fungi within one minute, in vitro, including mycobacteria, amoeba, and spores

WIDE USE OF CHLORINE DIOXIDE IN INDUSTRY

Paper mills in the U.S. generate an enormous quantity of ClO_2, 500 tons daily for bleaching pulp.[11] 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 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. ClO_2 does not adversely affect old paper prints or drawings, and will clean ancient documents without injury to fibers.

The first use of chlorine (Cl_2) as a water treatment process in the U.S. occurred in Jersey City in 1908 [12], and of chlorine dioxide, at Niagara Falls in 1944.[13] ClO_2 now purifies water in over 500 water treatment facilities in the U.S.[14] 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.[15] 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. 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.[16] The compound also removes cyanides, sulfides, aldehydes and mercaptans. ClO_2 as used in water disinfection is more sporicidal than Cl_2[17,18,] a more powerful inactivator of viruses[19], and inactivator of cysts and protozoan.[20] In storm water overflow, ClO_2 has proved active toward all viruses examined.[21]

Another application of ClO_2 is in the bleaching of fats and flour.[22]

> 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.[23]

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.[24,25] Flour treated with up to 500 ppm (5 times the concentration in DioxiCure Gel) fed to puppies had no untoward effect.[26] 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.[27] Flour bleached with normal dosage is not reduced appreciably in nutritive value.[28] Essential fatty acids are generally not effected, but tocopherol and cystine are oxidized.[29] Reactivities of 21 amino acids with ClO_2 were evaluated using an iodmetric assay, only 6 were found to be reactive at pH 6. They were cysteine, histidine, hydroxyproline, proline, tryptophan and tyrosine.[76]

Several other applications within the food industry have been described. The first reported use of 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.[30] When 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 ClO_2 is added to the wash water in order to maintain a 1 ppm residual.[31] 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.[32] The shelf life of tomatoes can be improved by treatment with ClO_2.[33] 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 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/1 (50 to 1000ppm) of ClO_2 or by exposure to air containing 2,000 to 3,000 ppm of 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 ClO_2. The preservation of melted cheese is facilitated by the addition of 100 to 300 mg/1 of ClO_2 to the milk used for its manufacture, and 100 to 400 mg/1 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/1 of ClO_2. The medicinal odor of cleaning shrimps is eliminated by adding 40 mg/1 to the washing water. A dose of less than 100 mg/1 of ClO_2 does not seem to hinder the taste or nutritive value.[34]

The remaining or residual products on fruits and vegetables after treatment with ClO_2 are apparently chloride and a trace amount of chlorite.[35] A patent by Frontier Pharmaceutical involves the lowering of the chlorite residual, and describes a method for the release of ClO_2 at higher, more physiological pH. Some industrial applications of ClO_2 other than bleaching or disinfecting include: the treatment of leather, where 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 [36,37] and neutralizing toxins [38]; 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. ClO_2 for example, does not combine with ammonia as does 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.[39] 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. In the human body, chlorite degrades mostly to chloride.

When purifying water supplies, 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.[40] 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 ClO_2 with algae, again, forms tasteless, odorless products. Olefins react much more rapidly with permangenate than with chlorine dioxide, whereas, triethylamine is thousands of times more reactive with chlorine dioxide than with permanganate.

Unlike most other oxidizing compounds, ClO_2, and its reduction product ClO_2^-, can act either as oxidizing or reducing agents. Under acid conditions hydrogen peroxide will reduce ClO_2 to form chlorous acid, but ClO_2 also can be oxidized by chlorine to produce chlorate, and by ozone to produce Cl_2O_6. ClO_2^- similarly can oxidize iodide to form iodine, or be oxidized by hypochlorite ion to form chlorate. Combining ClO_2 with blood causes methemoglobin by oxidizing Fe^2 to Fe^3 in the red blood cell. Breathing ClO_2 can have this effect.

When ClO_2 oxidizes organics, it usually takes in one electron and reduces to ClO_2^-. 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:

With most organics:

$$ClO_2\ (aq) + e^- = ClO_2^-\ \text{potential}\ E° = 0.95V$$

More active with some compounds:

$$ClO_2 + 5e^- = Cl + 2O^{2-}\ \text{potential}\ E^o = 1.5V$$

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

CHEMICAL REACTIONS [41,42,43,44]

Preparation of ClO_2

1. Acidification of chlorite

   $H^+ + NaClO_2 \rightarrow HClO_2 + Na^+$

   $5HClO_2 \rightarrow 4ClO_2 + HCl + 2H_2O$
2. Oxidation of chlorite by hypochlorite - for alkaline bleaching & water treatment

   $2NaClO_2 + NaOCl + H_2O \rightarrow 2ClO_2 + NaOH + HCl$
3. Oxidation of chlorite by chlorine

   $2NaClO_2 + Cl_2 \rightarrow 2ClO_2 + 2NaCl$
4. Reduction of chlorate with sulfur dioxide - used in pulp bleaching

   $2NaClO_3 + SO_2 \rightarrow 2ClO_2 + Na_2SO_4$
5. Oxidation of chlorite by persulfate

   $2NaClO_2 + Na_2S_2O_8 \rightarrow 2ClO_2 + 2Na_2SO_4$
6. Reduction & acidification of chlorate by oxalic acid

   $2HClO_3 + H_2C_2O_4 \rightarrow 2ClO_2 + 2CO_2 + 2H_2O$
7. Municipal Water Supplies

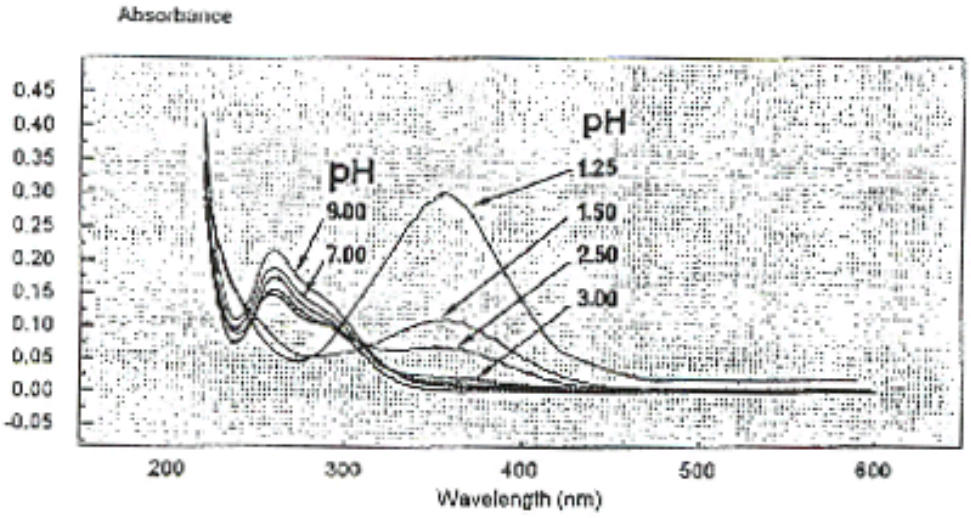
   $2HClO_2 + HOCl = HCl + H_2O + 2ClO_2$

To inhibit further oxidation, the following are good scavengers of ClO_2: sulfamic acid, sulfur dioxide, resorcinol, hydroquinone, sodium thiosulfate, sodium bisulfite, sodium sulfite, sodium arsenite and plumbous oxide. Agents that reduce 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.

Water solutions of ClO_2 will remain stable for several months if stored in a glass or PET bottle. Storage is increased in the dark, cool, and with no impurities in the water. Solution becomes progressively acidic:

$$6ClO_2 + 3H_2O = 5HClO_3 + HCl$$

"Stabilized" chlorine dioxide, which is a buffered solution of sodium chlorite, does not release ClO_2 until the pH of the solution is brought below 3:



UV-Vis absorption spectra showing the release of ClO_2 from sodium chlorite (buffered in the form of "stabilized chlorine dioxide") 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 ClO_2 at 360 nm. There is no release of ClO_2 above pH 3. from Multicomponent Spectroscopic Invetigations of Salivary Antioxidant,
Edward Lynch, Free Rad Res, Vol 26 p209-234, March 1997

Inorganic Reactions:

1. For iodometric analysis
   $$2ClO_2 + 2I^- \rightarrow 2ClO_2^- + I_2$$
2. Oxidation of iron
   $$ClO_2 + FeO + NaOH + H_2O \rightarrow Fe(OH)_3 + NaClO_2$$
3. Oxidation of manganese
   $$2ClO_2 + MnSO_4 + 4NaOH \rightarrow MnO_2 + 2NaClO_2 + Na_2SO_4 + 2H_2O$$
4. Oxidation of sodium sulfide

$2ClO_2 + 2Na_2S \rightarrow 2NaCl + Na_2SO_4 + S$

5. Oxidation of nitrogen oxide pollutant
   $2NO + ClO_2 + H_2O \rightarrow NO_2 + HNO_3 + HCl$
6. Gas phase reaction with flourine
   $F_2 + 2ClO_2 \rightarrow 2FClO_2$
7. In alkaline solution
   $2ClO_2 + 2OH^- \rightarrow ClO_2^- + ClO_3^- + H_2O$
8. Aluminum, magnesium, zinc & cadmium react with ClO_2
   $M + xClO_2 \rightarrow M(ClO_2)x$
9. Disproportionation of chlorite depends upon chlorides present, pH, and ratio of ingredients
   $4ClO_2^- + 4H^+ \rightarrow Cl^- + 2ClO_2 + ClO_3^- + 2H^+ + H_2O$
   $5ClO_2^- + 4H^+ \rightarrow 4ClO_2 + Cl^- + 2H_2O$
10. With hydrogen peroxide as a reducing agent in commercial production of chlorite
    $2ClO_2 + H_2O_2 + 2NaOH \rightarrow 2NaClO_2 + 2H_2O + O_2$
11. A highly colored complex is formed when ClO_2 is dissolved in an aqueous solution of barium chlorite
    $ClO_2 + ClO_2^- \rightarrow Cl_2O_4$

Organic Reactions:

1. With organic compounds in water → aldehydes, carboxylic acids, ketones & quinones
2. With olefins → aldehydes, epoxides, chlorohydrins, dichloro-derivatives, and chloro-and unsaturated ketones.
3. With ethylenic double bonds → ketones, epoxides, alcohols
4. With benzene → no reaction
5. With toluene → Ch_3, CH_2Cl, CH_2OH
6. With anthracene 45° → anthraquinone, 1, 4-dichloroanthracene
7. With phenanthrene → diphenic acid, 9-chlorophenanthrene
8. With 3, 4-benzopyrene → quinones, traces of chlorinated benzopyrene (no longer considered carcinogenic)
9. With carboxylic and sulfonic functions → no reaction
10. With aldehydes → 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
    $H_2O+(C_2H_5)_3N + 2ClO_2 \rightarrow (C_2H_5)_2NH + 2ClO_2^- + CH_3CHO + 2H^+$
14. With phenol → P-benzoquinone, 2 chlorobenzoquinone
15. Excess 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, phenylalamine, 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 CH_2OH → 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 napthaline → 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 C_8 are the most oxidizable by ClO_2.[45]
The organic compounds most reactive with ClO_2 are aliphatic tertiary amines, phenols, and aromatic amines
Unsaturated fatty acids and their esters are generally oxidized at the double bond.

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 NH_2 groups, amido and imido groups, HO groups in alcohols and HO acids, free or esterified CO_2H groups in mono and polybasic acids, nitrile groups, the CH_2 groups in homologous series, ring systems such as C_6H_6, $C_{10}H_8$, cyclohexane, and the salts of C_5H_5N, quinoline and piperidine.

Most aliphatic and aromatic hydrocarbons do not react with 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.[46] ClO_2^-, chlorite, the reduction product of 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.

DIOXIDERM AND DIOXIGUARD EXPERIMENTAL DISINFECTANTS

Studies have shown DIOXIGUARD and DIOXIDERM, which are ClO_2 or ClO_2 complexes, to be two of the fastest disinfectants.[47] Bacteria, viruses and even fungi are killed in under 1 minute in vitro. This rate of deactivation includes mycobacteria, amoeba and spores (non vacuum dried). Two questions immediately come to mind: How do these compounds 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.[48] [49] 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 and there appears to be no damage to whole structural components such as ribosomes.[50] 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.[51]

At high ClO_2 ppm, the method of rapid bacterial and viral kill appears to be the softening and destroying of the cell wall or viral capsid.[52] Human cells do not have similar cell walls and are apparently unaffected. Our skin and bodies are likely protected from the general oxidative effects of 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.

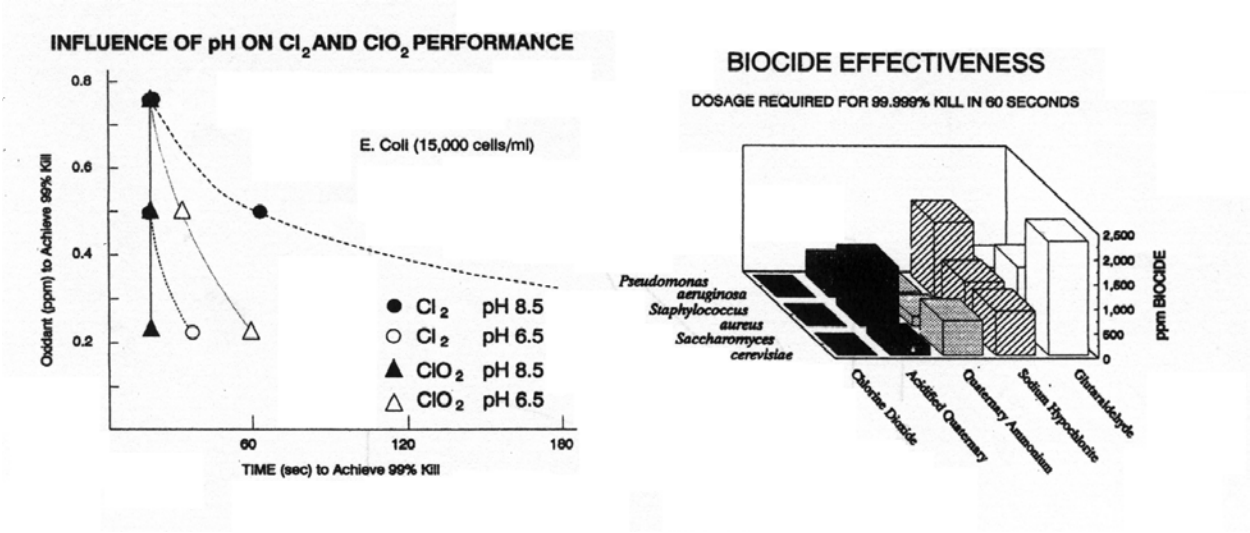
Because ClO_2 is a strong oxidizing agent and also itself a free radical, it quickly neutralizes reactive molecules, such as cytokines and oxygen free-radicals such as $NO^{\bullet}$, O_2^-, H_2O_2, HClO, and $OH^{\bullet}$ that are produced in the body by macrophages. These oxygen compounds are released 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 ClO_2, combined with its ability to completely disinfect, makes DIOXIDERM and DIOXIGUARD ideal wound medications. Unlike iodine compounds, or chlorhexidine, healing is not impeded.[53] [54] Veterinarians have been treating deep wounds and abscesses on tigers and elephants as well as dogs and cats with outstanding success.[55] DIOXIDERM GEL had similar striking results on human (otherwise non-healing) diabetic ulcers.[56] If our body could manage to manufacture chlorine dioxide, as it does hypochlorite, hydrogen peroxide and superoxide, it would probably do so.

ClO_2 is a small molecule relative to common organic disinfectants such as chlorhexidine, peracetic acid, and cetylperdinium chloride. It is also a gas, non-ionic, and soluble in water, oil, and organic solvents. These properties no doubt facilitate the transporting process through a bacterial cell wall, and aid in transporting through a bad wound.

It is interesting to speculate on the formation of a ClO_2 complex that may be involved in the disinfection process. Electron configuration of the ClO_2 molecule theoretically allows combination. ClO_2 will hydrate for example with water, and also can form compounds with the chlorite ion $[ClO_2 \bullet ClO_2^-]^-$.[57] A highly colored complex, $C_2O_4^-$, is formed when ClO_2 is dissolved in a solution of barium chlorite. There is evidence that more than one oxidant in the disinfectant formula will act synergistically in deactivating microorganisms,[58] 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 a chlorous acid complex (although unstable), and not chlorine dioxide, which is the more active of the two species. Chlorous acid has a higher oxidation/reduction potential than either 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 ClO_2 has many more times the oxidation power than ClO_2 alone at similar pH.[59] Interesting too, that the type of acid activator producing the chlorous acid molecule can have an effect on the oxidizing strength of ClO_2, or ClO_2 mixture. Comparison of the dosage required to achieve a 5 log reduction in viable bacteriaat a 60 second contact time using chlorine dioxide and chlorine at pHs at 6.5 and 8.5[62]

Disinfectant Comparison and pH Effect



NON-TOXICITY

Many evaluations have shown ClO_2 compounds to be non-toxic. Five decades of use have not indicated any adverse effects on health. The main areas of use has 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 ClO_2 in drinking water, additions to tissue culture, injections into the blood, seed disinfection[60,61], 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.[62]

In one tissue culture study, highly diluted DioxiDerm liquid was placed on CD4 cells infected with H.I.V. [63]. 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_2 disinfectant. No bacteria remained after this period, and the seeds then grew normally.[64]

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.[65] 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_2. 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_2 and ClO_2^- 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^- ion with a small amount of ClO_2^-. The no observed effect level, NOEL, from animal ingestion studies involving ClO_2 and ClO_2^-, ranges to 100 ppm [66,67,68], about the concentration of Frontier's DioxiDerm gel for topical use. The half life for the elimination of ClO_2 and ClO_2^- from the plasma is less than half that of HOCl, hypochlorite.[69]

In one study, human volunteers drank ClO_2 or ClO_2^- in solution up to 24 ppm and showed no adverse effects.[70] Several studies examined the effects on reproductive toxicity or teratology. There is no evidence of fetal malformation or birth defects at ClO_2 concentrations, in drinking as well as skin route, up to 100 ppm.[71 72 73] 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, hematacrit 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,[74] and honeybees,[75] were fed ClO_2 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_2 liquid and gel (similar to DIOXIDERM) were injected intradermally into guinea pigs, 10 times in about 3 weeks.[76] 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. Chlorhexidine and iodine compounds inhibit wound healing. Because both speed of deactivation and non-toxicity are combined in Frontier liquids and gels, new possibilities are opened for important topical products, as well as commercial surface disinfection.

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