OZONE, ENVIRONMENT POLLUTION AND THE EVIDENCE BASED MEDICINE

OZONO, CONTAMINACIÓN AMBIENTAL Y LA MEDICINA BASADA EN EVIDENCIAS

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Se describen las principales características del ozono. Su rol protector en la estratosfera; como agente contaminante en la troposfera e ingrediente esencial en terapias no demostradas. Se detallan los siguientes temas: el ozono en la estratosfera y la troposfera; como contaminante ambiental; obtención, almacenaje, medición y capacidad desinfectante; la Medicina Basada en la Evidencias (MBE) y las terapias con ozono; el ozono en México y Cuba. El ozono estratosférico protege la vida vegetal y animal de la radiación solar ultravioleta, mientras que el troposférico es un activo contaminante que daña la salud. A pesar de la gran cantidad de publicaciones sobre el tema, y según los criterios actuales sobre los ensayos clínicos y la MBE, no existen pruebas reconocidas por la comunidad científica mundial, ni fundamentos teóricos válidos, que sancionen la eficacia del ozono como medicamento.

The main features of ozone are reviewed. Its protecting role in the stratosphere, as a polluting agent in the troposphere and essential ingredient in unproven therapies. The following elements are discussed in detail: ozone in the stratosphere and troposphere; as a polluting agent; synthesis, storage, measurement and disinfectant capacity; the Evidence Based Medicine (EBM) and ozone therapies; the ozone in Mexico and Cuba. Stratospheric ozone protects animal and vegetal life from ultraviolet solar radiation, while the tropospheric is an active pollutant, harmful to health. In spite of the bulky amount of papers published on the subject, and in agreement with present criteria on clinical trials and the EBM, there are no proofs recognized by the scientific community, nor valid theoretical basis, endorsing the efficacy of ozone as a drug.

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I. OZONE IN THE STRATOSPHERE AND THE TROPOSPHERE

Ozone is an inorganic compound, gaseous at temperature environment, composed of three oxygen atoms (O_3). It forms form from recombination of molecules of atmospheric oxygen (O_2) under the action of sunlight. Its smell is reminiscent of chlorine and there are people with the ability to detect it at such small concentrations as 0.01 μmol/mol (1 mol = 6.023×10^{23} particles). However, odor is not a reliable index of its atmospheric concentration, due to olfactory fatigue that develops quickly. The following shows results of a bibliographic review that, in addition to the subject that this section, includes: Section II. Ozone as an environment pollutant; Section III. Production, storage, measurement and disinfecting capacity of ozone; Section IV. Evidence-based medicine and ozone therapies and Section V. Ozone in Mexico and Cuba.

Stratospheric ozone. Stratospheric ozone found in the ozone layer, about 20-30 km high and concentration of 2 to 8 parts per million, is formed by the absorption of solar radiation with wavelength λ between 200-240 nm, in a multi-stage process that can be represent as

$3O_2$ + solar radiation = $2O_3$.

The range of absorbed wavelengths belonging to the high energy ultraviolet (UV) region harms people and plants. The reverse reaction also takes place, since the least energetic UV radiation with λ up to 280 nanometers is capable of breaking up ozone molecules converting it to the original oxygen. That radiation, too harmful to living organisms, it is equally absorbed during the process. This creates a beneficial equilibrium for people, where ozone is continuously created and destroyed while absorbing harmful UV radiation earlier to landing [1]. In recent years, the fine balance between the formation and decomposition of stratospheric ozone was broken by the presence of contaminants, mostly by carbon fluorides used in refrigeration, with a direct threat to human health. The agreements of international organizations to prevent the proliferation of this evil have managed to limit and to some extent begin to reverse the process [2]. The concentration of ozone in the stratosphere is measured with spectrophotometers that can determine its concentration from the earth's surface. The first of they were designed by GMB Dobson in 1920 [3].

Tropospheric ozone. Ozone formation occurs in another way in the troposphere, closer to the earth's surface. Here ozone is bred under the action of visible sunlight, in a region with longer wavelengths and lower energy than the previous ones, but able of activate the reaction of the oxygen in the air with hydrocarbons and nitrogen oxides that come from

burning fuels. The total process can be expressed as:

O_2 + hydrocarbons + NO_x + visible light = O_3.

Also sources of environmental ozone are the workshops of electric arc welding, other areas where ozone is used as a disinfectant, any source of UV radiation, faxes, laser printers and photocopiers. Printers and modern photocopiers are equipped with ozone filters, which must be changed regularly. Like sparks are also capable of generating ozone from oxygen, it is estimated that the rays produce annually in the troposphere an amount equivalent to 10% of the ozone in the stratospheric layer.

II. OZONE AS AN ENVIRONMENT POLLUTANT

O_3 is a much more powerful oxidant than O_2, and has the property of attacking and disintegrating carbon bonds of many organic compounds, including vegetable and animal tissues. It may irritate the respiratory tract causing coughing, burning, wheezing, shortness of breath, and aggravate asthma and other ailments pulmonary; it is an important part of urban smog. Its effect is greater on hot and sunny days, where it can reach harmful levels. It is transported to large distances due to the wind and, for this reason, even rural areas can experience high levels of ozone coming from the cities. In Europe, the value of reference for hazardous ozone concentration in the outside is 90 nmol/mol (180 µg/m^3) [4].

Table 1. Effects of ozone on people (taken from reference [4]). 1 µg/m^3 ≈ 0.5 nmol/mol).

Concentration µg/kg	Effects
30	Perceptible to smell, with rapid habituation
70	Irritations in the ocular conjunctiva
100	Probable headache
160	Reduction of pulmonary bacterial resistance (determined in animals)
160-200	Pulmonary dysfunction, mainly when exercises are done
200	Increases de number of leukocytes
240-300	Increased frequency of asthma attacks
240-700	Physical strength reduction
400	Cough, chest pain. After 4 hours of exposure, hormonal and enzyme changes
800	Inflammatory reaction of tissues
1000	After 6-10 hours of exposure damage to human chromosomes appear

More sensitive to ozone are people with lung problems, older adults, people active outside home, outdoor workers and children. The latter are particularly sensitive, because their lungs are still developing and are more likely than adults to engage in outdoor activities. Also are more likely than adults to suffer from asthma [5,6]. Exposures to concentrations as small as 60 nmol/mol are capable of damaging the tissues of the system respiratory and plant tissues. In susceptible people smaller amounts (40 nmol/ mol) can cause chest pain, cough, shortness of breath, and throat irritations [7,8]. It can also worsen chronic respiratory conditions such as asthma and compromise the ability of body to fight infections in the apparatus respiratory (see Table 1).

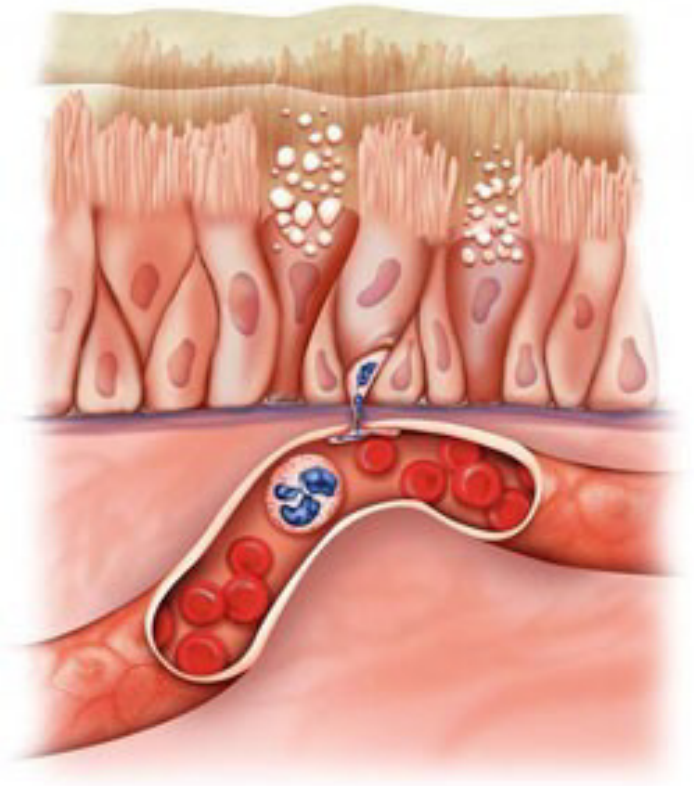

Figure 1. Along with the airway congestion due to ozone, a flow of white blood cells appears, and the formation of mucus fluid build-up and retention increase. This cause death and cell effusion in the airways. The process is comparable to inflammation of the skin caused by sunburn. (Taken from ref. [5])

When inhalation is brief, the disappearance of harmful effects usually occurs in a short time. There is less certainty about the persistence of the effects of prolonged inhalation or exposure to high levels. Environmental ozone can decrease lung function and inflame lung envelope. Repeated exposure can permanently damage lung tissues (Figure 1) [9-11]. A study conducted in the United States with 450,000 people with an 18-year follow-up resulted that in cities where there are large concentrations of ozone the increased death from lung disease raises by 30% [12,13]. In many countries the concentration of atmospheric ozone is regularly measured, alongside that of other gases capable of originating it, in places where its forming is more likely to occur, and warnings are released for the population (figure 2) [14].

Figure 2. Notice on the local environmental ozone situation (Houston, Texas). Taken from ref. [1].

Figure 3. The points show places where there are control centers of the Valencia Network for the Surveillance and Control of Atmospheric Pollution, in Spain, 51 in total. Taken from ref. [15]

Since ozone is continually created and decomposed into the atmosphere, its concentration can change rapidly, so it is usual to record the data in short intervals of time. For example, in Valencia (Spain), the data updated every hour are publicly accessible through internet, at the site www.cma.gva.es/atmosfera. Figure 3 shows the atmospheric pollutant detection network that exists in the Valencia Community [15]

III. PRODUCTION, STORAGE, MEASUREMENT AND OZONE DISINFECTING CAPACITY

III.1. Production in the laboratory

There are various methods to obtain ozone in the laboratory that include corona discharge tubes, the action of ultraviolet light or from water in a electrochemical cell. Corona discharge creates waste pollutants with nitrogen, while light is not very efficient. That is why in most cases the cell is preferable in most applications, as it provides a mixture of oxygen and ozone up to a maximum value of 20-30% O_3.

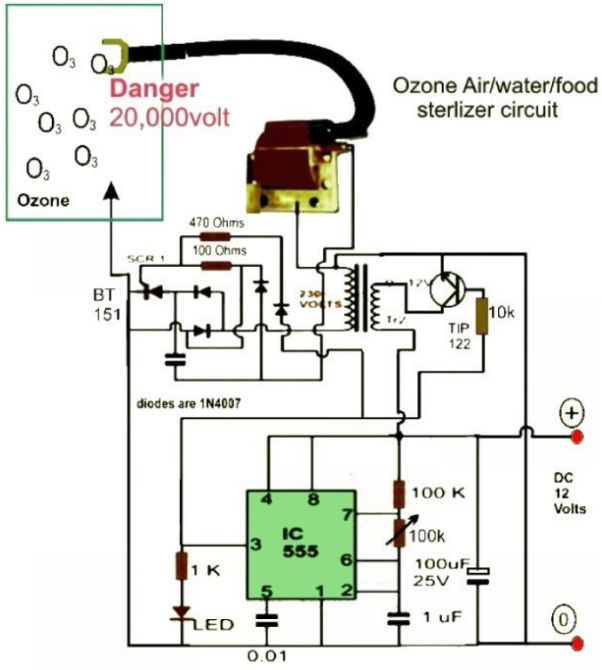

Figure 4. Circuit for an ozone electrochemical cell. Taken from https://electronicpowersupply.blogspot.com/2014/04/ozone-air-water-sterili-zer-circuit.html.

The optimal ratio requires high voltage values, and can vary remarkably depending on the current density in the cell, impurities present in the water, and the shape, size and materials of the electrodes [16]. Figure 4 shows a typical circuit for generating O_3. The applied voltage is about 20,000 volts.

Storage. Although there are theoretical estimates saying that trace amounts of ozone can persist in the atmosphere up to 22 days [17], the experimental results show its spontaneous decomposition to O_2 with a half an hour lifetime at 25 °C. It means that every 1/2 hour the ozone concentration is reduced by half, which means an approximate reduction of its concentration by $(1/2)^{48}$ times after a day (a fraction with 15 zeros after the point). If moisture is present, the half-life decreases noticeably; e.g., dissolved in water at 25 °C its average life time is reduced to 1/4 hour [18 ,19]. Hence, ozone cannot be stored and transported like any other industrial gas; once generated its concentration will be reduced to ridiculous values in a few hours. Any product that is promoted as

"Ozonized" in stores or pharmacies (being a soap, an oil, an ointment or any other) is a consumer deception, because when it reaches the retail market not even traces of the original ozone will remain but, in any case, only the products of its reaction with other ingredients.

III.2. Ozone concentration measurement

Measurement methods in the troposphere include ultraviolet absorption, differential optical absorption spectroscopy, chemiluminescence, LIDAR (from the English Light Detection and Ranging) and various chemical methods of titration as the colorimetric tube [20 ,21]. One of these commercial instruments, used to measure concentration in workplaces, it is based on indigo blue (indigotine), that in the presence of ozone it oxidizes to isatin ($C_8H_5NO_2$) of white color. The air is drawn in by means of a plunger into a disposable capsule with calibrated ranges of coloring (Figure 5).

Figure 5. Local measurement of environmental ozone. Dräger ozone detector tubes and Accuro hand suction pump. Taken from ref. [4]

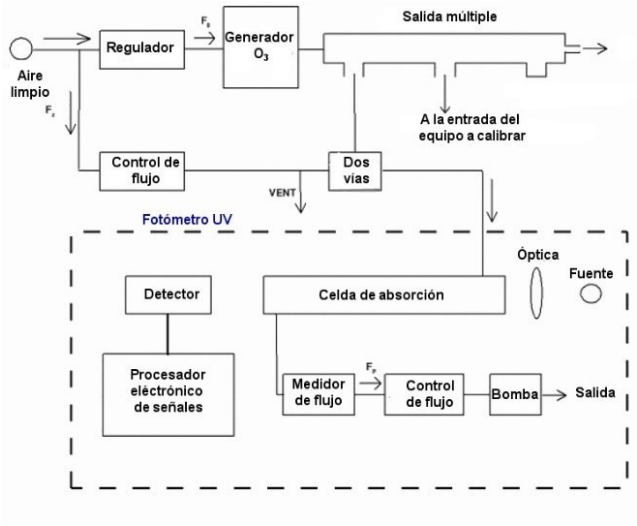

Figure 6. Typical concentration photometric UV calibration system ozone. Measures the paperwork at 254 nm with an uncertainty of 3% and pressure and temperature controls (translated from [23])

The standard comparison pattern is the Reference Standard Photometer of the National Institute of Standards and Technology NIST, endorsed by the International Bureau of Weights and Measures [22]. It is used to calibrate secondary standards, which in turn are used to adjust the measurement systems of numerous environmental ozone monitoring networks throughout the world. Figure 6 shows one of several possible schematics of a typical UV ozone concentration photometric calibration system [23]. Other systems for automatic measurement by chemiluminescence appear in the same reference.

Disinfectant capacity. Produced on the spot is used as a cleaning, disinfectant and deodorizing agent in a myriad of applications, (food, water, clothing, instruments, pools and many more) [1]. Also in hospitals, to decontaminate operating rooms: after the usual disinfection, the room is sealed and filled with ozone to neutralize any remaining bacteria [24].

IV. THE BASED ON EVIDENCE MEDICINE AND OZONE THERAPIES

Starting in the 80s of the last century, the concept of "Evidence Based Medicine" (EBM) generalized worldwide; it considered so far insufficient the traditional pathophysiological reasoning to take clinical decisions. As pioneers in the development of EBM the published works of Archie Cochrane, John Wennenberg, Ivan Ilyich and Thomas McKeown from the 1970s are acknowledged [25]. The points to be considered by the EBM are:

- The search and discovery of the biomedical literature original and relevant and its critical and correct reading interpretation to establish the actual level of evidence.
- Clinical experience and systematic knowledge of the context of that experience.
- The preferences of the patient.

The Cochrane Collaboration is a non-profit organization made up of around 11,500 researchers from about 90 countries that apply a systematic and rigorous review process of health publications. Results are regularly published in the Cochrane Library [26,27]. Some consider that together with the Nuremberg Code [28] and the Declaration of Helsinki [29], the concept of MBE created bases for a true social revolution in the field of the medicine of the last century. Regarding ozone, no Cochrane favorable results appear yet. On the contrary, negative results do appear in various places. In 2005 a Committee of Experts of the Malaysian Ministry of Health concluded that there was no evidence to recommend the therapies of ozone as an alternative treatment in none of the diseases analyzed (AIDS, ischemia, ophthalmology, otorhinolaryngology, gynecology and obstetrics, orthopedics, cancer and dermatology) [30].

In the US, the federal regulatory code dated April 1, 2016, in its section (a) it states the following: "The ozone is a toxic gas with no known medical applications; specific, adjuvant or preventive"(sic) [31]. In the following sections, the regulatory code provides details about its harmful effects and considers ozone generators fraudulent if used in hospitals or other places for sick people. Another reference states that there is no evidence credible, peer-reviewed, supporting ozone as a type of medical therapy [32].

However, there are many who apply ozone therapies attributing to this gas all kinds of beneficial effects, but not mentioning the possible damages it can cause. For example, it is argued that ozone is capable of oxygenating tissues in a beneficial way. But a critical report published on the internet in 2001, with 59 scientific journal references, report that when ozone is introduced into the blood reacts with the water in the red blood cells generating hydrogen peroxide and also bactericidal free radicals that cause damage to the cell membrane. A bibliography search carried out in 1995 in the Medline databases, Health, Aidsline and Cancerlit provided over 100 articles, from 1966 to that date, reporting effects adverse effects of ozone or its reaction products, both in humans as well as in experimental animals [33].

The report also concludes that the ingestion, infusion or hydrogen peroxide injections cannot re-oxygenate body tissues by the following: metabolism of a 60 kg adult requires 200 to 250 ml of oxygen per minute, a need that is covered by the normal breathing [34]. Every liter of blood that comes out of the lungs carries about 200 ml of oxygen, of which about 50 ml are absorbed when it passes through the capillaries in tissues. It has been estimated that during a conventional ozone therapy session the amount of oxygen that comes from the decomposition of ozone does not exceed 4 ml per hour (about 0.7 ml per minute), so the possible contribution to tissue oxygenation is negligible when compared to that of the oxygen that comes from respiration [35].

Regarding the possibility of applying it to people like disinfectant, the Environmental Protection Agency of the United States (EPA), has stated that there is "... evidence that at concentrations not exceeding public health standards, ozone is not effective in remove ...viruses, bacteria, fungi or other biological contaminants". For ozone to be effective as a germicide must be present in a concentration much greater than that safely tolerated by humans and animals (ref. [31]).

The EPA has also issued repeated warnings about commercial ozone generators sold with the purpose of purify homes and offices. A report published in 2008 warns about the falsity of an advertisement proclaiming that these devices had been approved by the US federal government [36].

Ozone therapies are not allowed in the US since long time ago. Already in 1998 a couple that claimed health benefits when marketing ozone generators without scientific studies to support them, was sent to prison for fraud in a US federal jury [37]. The Food and Drug Administration FDA maintains in that country a permanent surveillance on this type of fraud; a press release from January 2010 reported the performance of US Marshals in the appropriation of 77 ozone generators from a California company, after being previously warned to suspend sales of generators designed for medical applications [38]. Canada has also similar bans about the use of ozone generators, although somewhat less rigorous than in USA [39,40].

The main international criticisms about ozone therapies in essence cite arguments similar to those alleged by the North American agencies: the absence of scientific studies demonstrating the proposals of their supporters [30,31,41]. Another argument used by ozone sympathizers is that, in some way (not known and much less proven), ozone is able to stimulate the body to provide a curative response to the condition do you wish to intervene [42]. This argument is used to treat to justify its application to very dissimilar problems, and is equivalent to consider that the gas is capable of recognizing what is not working in the correct way and make the natural means of defense of the body more efficient to combat that specific disease, but without affecting other processes or organs.

Since no one has proven the existence of the proposed mechanism of action, it is usual that in order to validate the proposal their promoters will present some illusory assumption as if it were true (something common in all pseudosciences). Hypotheses proliferate, but there are no valid theories, although sometimes they are quoted as if they were true. They also propose fuzzy arguments and vague generalizations like "improves quality of life" or "increases immune response of the organism", without further explanation. A detailed review of the literature shows that it is usual for those who promote ozone therapies consider valid references that are not scientific; or report investigations that generally do not meet the minimum requirements established to validate clinical trials which disregard control groups that would serve to compare results, as is usual in any randomized clinical trial. The data on applied ozone concentrations; at most, usually talk about volumes of gaseous mixtures of ozone and oxygen (in unknown proportion). Their therapies are applied indiscriminately to any ailment, from cavities to cancer to AIDS, giving rise to a large number of supposedly scientific articles. It is very uncommon to find reports of side effects or contraindications; there are no negative reports, instead their results are always positive or "promising". Google Scholar shows more of 4,000 entries on ozone therapies from 2016 to February 2017.

In view of the expressed before, more than citing and refuting the abundance of spurious reports or unsubstantiated claims published by ozone promoters, it seems appropriate to comment on some review articles on the subject, written by those who obviously favor these therapies.

IV.1. Review articles

In a summary of Elvis and Etka from 2011, when mentioning the effectiveness of ozone to control infections in people along with its anti-inflammatory properties cite an article of more than 100 years ago, without mentioning later criticisms [43,44]. The article alludes to the use of "precise therapeutic doses "without specifying what those doses are or how they are they measured, which is usual in this type of report. In fact, in the bibliographic review carried out to write this article it was not possible to find even one report that mentioned the method used to measure the concentration or ozone doses supplied to patients. As it happens with any other medication, the amount and strength applied are essential parameters to evaluate the efficacy of treatment and determine safe levels and harmful effects, possible recommendations, side effects and contraindications. This information is also essential for other researchers could reproduce the treatment and vouch for its effectiveness (or deny it).

The figure 1 that appears in the summary of Elvis and Etka [25-27], tries to represent the mechanisms of action of ozone in the organism. However, the reference [26] refers to website titled *holistic-bodyworker*, obviously divorced of science; in its original version, holism is a philosophical current created by the South African Jan Smuts in the first half of the last century, which is often deformed to the esoteric [45]. The other two articles cited are: one, on "theoretical considerations" without any experiment; the other is taken from a website of a particular user, not from any peer-reviewed journal or known research center. Hence it is not possible to attribute any truth to that figure, which, furthermore, immediately casts doubt on the scientific reliability of the authors and all the content of their review article.

Elvis and Etka mention some clinical trials, but not even a single finished one that demonstrates ozone benefits (their references 30-35). However, later on the "advantages of ozone therapy" are discussed (citing references [36-38, 40]), when in fact only one of those articles mentions supposed benefits for people. The remainder refers to animal tests, lung damage, not proven hypotheses, the effect on isolated AIDS viruses or antibacterial effects, but not in humans.

Another reference worth citing corresponds to a statistical meta-analysis of Magalhaes et. al., which reports an exhaustive search on the effects of applied ozone in the spine from 1966 to 2011 [46]. But it is also recognized in the article itself that it does not exist even a single report where, along with the application of the ozone, the effect of a placebo were taken into account in a control group. Therefore, this meta-analysis is performed from biased or imperfect data and is not capable of discern whether the therapy provided a greater benefit than of the placebo or if its application actually slowed the natural process of pain relief or disease cure.

Given the highly aggressive nature of ozone on tissues, this last possibility cannot be ruled out. To this we should add the well-known ignorance of the doses applied, -by not specifying concentration, the authors do not can tell if O_3 was actually applied in amounts of therapeutic significance, or just O_2 was applied. Really, the only thing clear from the authors' own exposition is that their article represents an unquestionable example of the use incorrect statistics to try to justify what is not.

Something similar occurs in another meta-analysis, also from 2010, where the authors attest to the effectiveness of the treatment of ozone for lumbar hernia, but there is talk of the application 1 to 9 ml of oxygen/ozone mixtures without stating proportions, not verifying if they were the same in all cases, and even if there is certainty of the existence of any ozone in the injected mixture [47]. The article states that ozone has analgesic and anti-inflammatory effects, which nobody has demonstrated, but it does not refer to the fact that it is a potent irritant to tissues, which has been widely made known (section 4).

V. OZONE IN MEXICO AND CUBA

Despite multiple international criticisms and the existing prohibition in Canada and USA to commercialize ozone generators for medical applications, in neighboring countries such as Mexico and Cuba ozone therapies are applied generously and indiscriminately.

V.1. Mexico

In 2013 Mexico was the second country in Latin America with highest number of deaths due to environmental pollution (15 000 per year, according to the World Health Organization's statistics) [48]. Currently there are in Ciudad Mexico and in the state of Mexico a total of 29 automatic monitoring stations, and the air quality is reported every hour through the site www.aire.cdmx.gob.mx; ozone is one of the monitored pollutants [49,50].

However, despite the sensitivity that exists in Mexico about the environmental problem, and in particular with ozone, the Mexican press outlined in 2015 the legal efforts of the promoters of ozone therapy for legalizing it. As a curious note, the Cuban Society of Ozone-therapy, a foreign entity in Mexico, was also part of the request to the Health Commission of the Mexican state [51]. According to the Mexican press, Cuba is the only country, after Russia, which has legalized and regulated the practice of ozone therapy [52].

V.2. Cuba

The bibliographic search on the monitoring of environmental ozone found only one report from the Group Interdisciplinary Institute of Meteorology (INSMET) on tropospheric ozone from February 2014. This report only shows general details on a group of provinces, without reporting local concentrations [53]. In 2016 the official newspaper Granma stated that atmospheric decontamination is a "matter of priority for Cuba", and that there is an INSMET project to monitor all the country gas emissions. Carbon oxides, nitrogen and sulfur, but not ozone specifically [54].

Contrary to what one might think, the Center for Ozone Investigations, founded in May 1994, is not devoted to recording information and statistics on the stratospheric ozone or the effects of ambient ozone on the population, information not accessible in the country. Is dedicated to produce ozone generators brands OZOMED, OZONEY and AQOZO, electrolytic and by corona discharge, to medical, industrial and social uses at homes, cafeterias, etc. (The same ones forbidden in USA and Canada, section 4). Also devotes to applying ozone-therapy to the population, free of charge, for the treatment of very diverse ailments [55]. For many years Cuba has been the American country where there is a greater diffusion of therapies with ozone with official support. An editorial from 2013 in the Revista Cubana de Farmacia declares that "the first research center on ozone was founded in Cuba", without further details [56]. Cuban ozone therapy even has the apparent endorsement of the Pan-American Health Organization PAHO. On the Cuba page of PAHO appears a set of unproven therapies under the title of 'Natural and Traditional Medicine' among which you can find ozone therapy (and also homeopathy and others not recognized by conventional medicine) [57]. It seems quite evident that this contradicts at least one PAHO publication aimed at the general population, which describes with quite enough details how treatments should be tested [58]. Y perhaps also with the declaration of Helsinki, promoted initially in 1948 by the World Medical Association. In 2013, this association had 102 medical societies and about 10 million members [59]. The WMA is currently developing the campaign "Be Aware" against false medicines and in favor of secure information to colleagues and patients. The WMA believes that false drugs can cause effects harmful to the patients, including death in the worst case cases, and undermine public health efforts in countries pressed by limited resources [60]. The literature review revealed multiple national research reports on ozone therapies although, apparently, these investigations never maintained close collaboration with the dependencies of the Ministry of Public Health in charge of guiding and controlling clinical trials to ensure their validity and patient protection. The above is inferred from a search carried out in January 2014 in the Cuban Registry of Clinical Trials, which did not show a single inscription where ozone is mentioned [61,62]. The aforementioned editorial of the pharmacy magazine expresses that the first experiments with people were carried out in 1998, and refers to what he considers "successes in the treatment of pigmented retinitis, glaucoma, retinopathies and conjunctivitis (...) published in Cuba by a group of researchers", citing the confusing claim that "an oxidizing agent how ozone can induce an antioxidant effect ", without give even hints of the possible mechanism or the supposed redox reactions that would take place to justify this hypothesis [63,64].

On the INFOMED WEB site of the Ministry of Public Health you can find a book and no less than 20 articles published on ozone in human research, reporting improvements in very diverse ailments [65-83]. The detailed review showed that the usual and common to all of them is that the characteristics described in section IV: no control groups, no measurements, and no report of applied concentrations. Assuming the supposed efficacy of the treatment were true, the lack of basic information prevents the reproducibility and verification of these results by other researchers. In some cases the application of ozone was carried out jointly with other treatments, further increasing the uncertainty of the procedure.

Misleading reports sometimes appear, such as promoting oils or other "ozonized" products, where ozone is actually one of the reactants involved in the process, and not a reaction product. Those products include ozonides, hydroxyhydroperoxides, hydrogen and aldehydes according to ref. [60]. However, only 4 ozonides are known: KO_3, CsO_3, NaO_3, LiO_3, unstable and explosives in their pure state and without therapeutic properties known [84]. Given the short half-life of the ozone, it is not possible that after a few hours even traces of residual ozone remain in the supposedly ozonized medicine.

The burden on the public purse caused by the widespread and gratuitous application of this therapy cannot be despise, because despite the absence of a demonstration valid of its effectiveness, its use was extended by countless assistance centers throughout the country. Only in one of these centers, in a report covering the years 1993 to 1997 appears that 1960 patients were treated rectally, intravenous or muscular, with an estimated cost of 660,000 pesos [85]. Personal interviews with various patients carried out by the authors indicate that it is common that basic ethical standards for testing are observed clinics, where informed consent is paramount [86]; those who apply the therapy consider it valid and not advise the patient that it is not a recognized procedure worldwide and has even been declared worthless and banned in other countries. Something similar happens with alleged ozonized products, apparently arising from a local initiative (ref. [60].

It is impossible to bring together the reported evidence on the effect of environmental ozone with claims of ozone therapists, who report benefits on tissues by blowing it directly into the skin, eyes, ears, or inside the body: in the spine vertebral, vagina, rectum ... the airways! or by bubbling ozone into the drawn blood for later re-injecting it. As is never reported something so essential as the figures of the concentrations applied to the patients, the recurrent absence of pharmacodynamics and pharmacokinetics studies becomes noticeable, as can be inferred from several review

articles where these data is never mentioned.

VI. CONCLUSIONS

Stratospheric ozone protects plant and animal life from harmful ultraviolet radiation, while tropospheric it is an active polluting that damages health and its emission is subject to regulations in many countries. Until today in Cuba there are no systematic local reports to the population of tropospheric ozone concentration or other pollutants. According to the procedures recommended by WHO and other agencies such as the Cochrane Collaboration or the FDA in the USA, there is no evidence to validate the efficacy of the ozone as a medicine. Nor there is any theory that justifies its supposed curative effects; everything remains on hypotheses or assumptions not supported by the experiment, difficult to accept when they refer to such dissimilar ailments. A vision that reflects with crystal clarity the concerns on clinical, scientific, academic, ethical and protection of the patient of contemporary ozone therapists is obtained by comparing the drug definition that appears in the multiple editions of the well-known Goodman and Gilman text "Pharmacological Basis of Therapeutics" with the criteria from a notorious contemporary ozone therapist. According to G and G, a drug is "...any substance that produces effects measurable or sensitive in living organisms and that is absorbed, can be transformed, stored or eliminated". But for A. Schwartz, gynecologist and president of the Spanish Association of Medical Professionals in Ozone Therapy, also president of the International Medical Ozone Federation and director of a clinic of the ozone in Honduras: "…ozone is not a drug and as such does not cause collateral effects "(sic). [87].

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