

Ancona, Italy
May 25, 2011

To:

Edward Calabrese, Editor in Chief *Dose-Response*
and
Denise Leonard, Managing Editor *Dose-Response*

Subject: "Ozone as U-Shaped Dose Responses Molecules (Hormetins)," *Dose-Response*,
9:32–49, 2011. Replay to the allegation of plagiarism.

Dear Doctors,

We hope this letter find you in your best moment. We really feel honoured to know that a scientist of your calibre is acting as the editor of the journal we have selected to submit our manuscript.

Please, find enclose our explanation to the allegation of plagiarism submitted to Dose-Response Editorial board. We hope that with this argument you can get your own opinion. We are also sure that your final decision will be the best judgment, and we will respect it.

Thanks for your kind attention,



Prof. Gregorio Martínez-Sánchez, Pharm D., Ph.D.
Pharmacologist, Senior Research



Prof. Lamberto Re, M.D.
Medical Doctor, Ph.D.

1. Background

First of all, I would like to cite a phrase once remarked by José Martí Pérez (January 28, 1853 – May 19, 1895; was a Cuban national hero): “**all the glory in the world fits in a kernel of corn**”. Through this introductory comment you will find the real intention of the person we suspect had sent you the allegation of plagiarism.

The first person who mentioned the association of ozone and the term *Hormesis* (in medicine application) was Dr. Lamberto Re (author of the manuscript in *Dose Response*): *Re L. La Terapia con Ossigeno Ozono o Ozormesi: recenti acquisizioni scientifiche. 2008*.¹ The comment that associated the concept of hormesis was first mentioned in this journal even when the same phenomenon was previously described as *oxidative pre-conditioning* (León, 1998)² and successively used with this name for many years.

The aim of the review in *Dose Response* (2011) was to call the attention of the reader about the applicability of this phenomena and its conceptualization in ozone therapy. By the first time was associated the behavior of ozone in therapy with the concept *hormetin*. We consider this review as an *analytical review*, because not only summarized and up-date the main elements to support the association of ozone therapy with the concept *hormetin*, but original Fig. 1 and 2 hypothesized and summarized the explanation addressed in the text body.

The manuscript was send it on January 4th, 2010, submitted to a reviewers consideration (18th March 2010), amended and subsequently approved and published *on line* during 2010 and now assigned to: Volume 9, Number 1 / 2011 with a Relevancy index of: 23.0%.

On December 12th, 2010 Dr. Martínez-Sánchez received the manuscript entitle: OZONE ACTING ON HUMAN BLOOD YIELDS A HORMETIC DOSE-RESPONSE RELATIONSHIP by Velio Bocci, Lacopo Zanardi and Valter Travagli from the editorial board of *Journal of Translational Medicine*. They asked him to act as a referee. On December 28th he sent the referee report suggesting minor changes. The amended manuscript was resent by the editorial board of JTM on February 2011 and also the criteria of the 5 blind referees. One of the referees did an extensive analysis of the paper and suggests: [...] *Page 12. Ozone Therapy Section. A good opportunity to introduce a quantitative discussion would be with the introduction of the studies by Martin-Sanchez et al. A quantitative discussion of these results is noticeably absent.... [...]*.

Indeed, the amended manuscript was a “self plagiarism” with the introduction of brief tendentious comment as:

1)...*In Countries such as Cuba, Russia, China and India treatments by ozone are already a reality, although doubtful administration modalities are in current use....*

Or:

2)... *Martinez-Sanchez et al. have also reported that the theoretical U-shaped curve fits the ozone therapy results, but they do not comment specific situations.....*

Evidently the main author supposed that the blind referee was Dr. Martínez Sánchez, and introduces unethical opinions about the science produced in Cuba and other countries and against the article (at that time in press) in Drug Response. Dr. Martínez Sánchez replied to the editor of *Journal of Translational Medicine*:

1)...It is reported the use of ozone in several countries, after that, an extended discredit dissertation is done about the methods used. This paragraph has no sense in this manuscript; in addition ignore the published clinical results reached by scientists from these countries. Its sound as a discriminatory dissertations and I suggest canceling this paragraph....

2) ... Comments about the paper of Martinez et al. were not right, they are based on real facts, and specific examples appeared. For example, Fig. 3 took data from: Bocci, V. 2005. Ozone A New Medical Drug. Springer, Dordrecht, The Netherlands.....

For the final version of this article³ authors were forced to cite the paper in Dose Response and eliminate or moderate their tendentious comments.

On February 18th, 2011 I received and E-mail from Prof. Bocci, and I responded properly:

Dear Dr Martinez-Sánchez,

When a few months ago we submitted our paper to J.T.R., one referee asked to comment your cited paper that you have presumably written and published on Dose-Response. Thus I read it again and I would like to thank you for the numerous citations. However, quite frankly, I was a bit disturbed by the fact that you reported whole sentences literally copied from my books or reviews. Just a few examples:

Pag 3 " The ozone treatment is now envisaged as a transitory..." and "if the disease has gone too far"..

Pag 8 at the bottom: " So far the most advanced.." Nobody else except myself has never used "the stoichiometric fashion.." terminology

Pag 9 The strongly oxidized blood, including the foam... " and little later : " ozone doses are always applied by the physician using the strategy: start low, go slow.." This is an expression that I wrote the first time and published in my 2002 book.

I am glad that you used my expressions because obviously you appreciated them but, as I am an old scientist, allows me to suggest that when you report sentences of other authors, you should always include them within inverted commas plus their relative source.

Best regards , Velio Bocci

Response:

Dear Prof. Bocci

First of all I would like to thank your e-mail, your sincerity and honesty. You are the inspiration of most of the scientist that will go on in the file of O3 research. I was requested to act as a reviewer of your manuscript sent to JTR some months ago. I did some minors comments, but at that time the reference to my manuscript in Dose Response was already included in your MS. Our manuscript was accepted by Eduard Calabrese some months ago, already available on line, and will appear in the printed version of the Journal probably on March 2011.

G. Martínez- Sánchez, L. Re, A. Giuliani, and G. Pérez-Davison. OZONE AS U-SHAPED DOSE RESPONSES MOLECULES (HORMETINS).

In fact, I appreciate a lot your entire job and expressions. The manuscript includes 11 references (14 %) of your job of a total of 78 references. Even if there is any involuntary omission, I think that is very positive that the paper was accepted by the pioneer of the hormesis, and is a good thing for all ozone/therapist. I apologize for the omissions of the reference in these sentences, but you should know that all the scientist in this field know clearly that those phrases are coined by Bocci, no by Sanchez even when any punctual reference could not was cited. As always, it is an honor for me to hear your comments, suggestions and tips. We still should learn a lot about your job and scientific experience.

Sincerely,

On May 17th, 2011 I received from Denise Leonard, Managing Editor of Dose Response, an E-mail concerning the allegation of plagiarism. It is relative easy to suppose who was the author or at least the promoter, his motivations and scope. Evidently, he is someone who finds the **glory** at any price. I am sorry for this long introductory comment, but I think that explains in part the background of this unpleasant situation.

2. Analysis part by part of the Review

First to begin a step by step analysis of the highlighted comments in the manuscript I would like to introduce the concept of Scientific **Review**.

How is a Review? (according to Robert Day).⁴

A review paper **is not an original publication**. On occasion, a review will contain new data (from the author's own laboratory) that have not yet appeared in a primary journal. However, **the purpose of a review paper is to review previously published literature and to put into some kind of perspective**.

A review article is usually long, typically ranging between 10 and 50 printed pages. (Some journals now print short "minireview"). The subject is fairly general, compared with that of research paper. And **the literature review is, of course, the principal product**. However, the **really good review** paper are much more than annotated bibliographies. **Offer a critical evaluation of published literature, and often provide important conclusions based on that literature**.

According to this, our current review fits this concept.

2.1. Abstract

According to the highlighted items the abstract (193 words) was written using a mixture content of 6 reprint. Sorry, but I may say that from the beginning this highlighted items seems to be done by a unprofessional. Just two examples:

- 1 “*Health benefit*” is supposed to be copied from:
Ageing Res Rev. 2008 Jan;7(1):43-8. Epub 2007

We did the following experiment: to write in Google search bar “*Health benefit*” (write exactly like that). The result: 254 millions of records appeared. Surprise! There are 254 millions of plagiarisms of this grammatical construction; we are not the only ones.

2. “*can be induced as a consequence of an adaptive cellular stress response*” is supposed to be copied from: Ageing Res Rev. 2008 Jan;7(1):43-8. Epub 2007

Using the same methods followed in the experiment 1, the result of Google search was: Only one record contains the same grammatical construction. Surprise! It is the article in Dose Response: 2010 May 10; 9(1):32-49. Then, we have the glory and the copyright of this grammatical construction.

3. Highlighted No. 3 and No. 4 is supposed to be copied from: Ageing Res Rev. 2008 Jan; 7(1):63-78. Epub 2007 Aug 31. It is easily to find a none exactly but quite similar grammatical construction also in:

Hormesis: A Revolution in Biology, Toxicology and Medicine, 2011 from Mark P. Mattson, Edward J. Calabrese.

And

Animal Models of Human Cognitive Aging and Aging Medicine, 2009, 1-28, From Nicole C. Berchtold and Carl W. Cotman

Remarks: Scientists who work in hormetic science became practice the plagiarism each other? Or maybe terms as hormesis, hormetic amplification, homeodynamic space, nutritional hormesis, etc. became part of their language and became used more frequently?

4. Highlighted No. 5 supposed to be copied from: Ageing Res Rev. 2008 Jan;7(1):63-78. Epub 2007. Even when constructions are similar, the senses of the sentences are completely different and mean different concepts, and then we could not cite Rattan.

Rattan: The established scientific foundations of hormesis are ready to pave the way for new and effective approaches **in aging research and intervention**

Martinez et al.: The established scientific foundations of hormesis are ready to pave the way for new and effective approaches **in redox related disease research and intervention; ozone therapy can be a good candidate.**

2.1. Introduction

Supposed to be integral copied from:

- 1 Environ Health Perspect. **2006** Nov;114(11):1631-5.
- 2 Ageing Res Rev. **2008** Jan;7(1):43-8. Epub 2007 Sep 1. Review.
- 3 Bocci *et al.* 2009. Med Res Rev. **2009** Jul;29(4):646-82.

Just note that the followed references cited in **Introduction** sections are not cited in Bocci *et al.* 2009, and of course not appeared in references 1. Environ Health Perspect. **2006** Nov;114(11):1631-5. or 2. Environ Health Perspect. **2006** Nov;114(11):1631-5, just because those paper was done before 2008-2009. Also note that references using in the introduction from i) to j) were from our own authorship (Lamberto Re and Gregorio Martínez-Sanchez). In addition, elements took from Bocci *et al.* 2009 were already cited. Summarizing, this is a genuine introductory up-date. In the last paragraph (54 words) in introduction (aims) is curious to note that is supposed to be copied from 4 different sources (big mistake). The only word that it supposed not copied was “ozone”.

- a) Calabrese and Blain 2009
- b) Zhang *et al.* 2009
- c) Rattan *et al.* 2009
- d) Shanker 2008
- e) Cox 2009
- f) Radak *et al.* 2008
- g) Loncar *et al.* 2009
- h) Bocci *et al.* 2009
- i) Re *et al.* 2008a
- j) Re *et al.* 2008b
- k) Martinez-Sanchez *et al.* 2005

2.2. The paradox of ozone

1. The first paragraph is assumed took from: Med Res Rev. 2009 Jul;29(4):646-82.

These paragraph was took with a small modification from Bocci 2002⁵ and cited at the end of the paragraph.

[...]can transmit to all organs the information of an acute oxidative stress (Bocci, 2002).

2. The second paragraph and one sentence in paragraph 2 are assumed took from: Med Res Rev. 2009 Jul;29(4):646-82.
Cardiovasc Hematol Disord Drug Targets. 2009 Jun;9(2):78-85.

It was originally take and modified from: Bocci, 2006⁶ and Ross and Hu 2003,⁷ and cited and the end of the second sentence of the paragraph 3:

[...]Therapeutic dose of ozone can up-regulate the synthesis of antioxidant enzymes and hemoxigenase 1 (Ross and Hu, 2003; **Bocci, 2006**) [...]

3. Page 36 and table 1, is supposed to be copied from:

Bocci, Ozone. A new medical drug. Dordrecht, The Netherlands: Springer, 2005.

Part of the text was took from Bocci 2006 and properly cited:

[...] biochemical and metabolic conditions (**Bocci 2006**).

Information to elaborate Table 1 was took from the book Bocci 2005, but modified. In the book units are expressed in *ppmv*, in the Drug Response manuscript in $\mu\text{g/L}$, note and capititation are genuine and different from the book.

4. Page 37/ 39 is supposed to be copied from:

Lippmann M. Nonlinearity Biol Toxicol Med. **2005** Jan;3(1):125-44.

And Bocci. Bocci, Ozone. A new medical drug. Dordrecht, The Netherlands: Springer, **2005**.

Note that in this fragment the ideas are up-date using reference post 2005.

Yamazaki et al. 2009

Chuang et al. 2009

Lippmann is also cited properly:

Page 37 [...] chronic obstructive pulmonary disease (**Lippmann et al. 2000**) [...]

Page 39 [...] appears to be reasonable and prudent (**Lippmann 2005**) [...]

The paper of Lippmann (2000 and 2005) was about the toxicity of O₃ when inhaled. We used, updated and adapted his data and part of his analysis to illustrate this phenomena in this segment of the paper. It is just a review.

5. Page 39/41 is supposed to be copied from:

Bocci, Med Res Rev. 2009 Jul;29(4):646-82.

Bocci, Arch Med Res. 2006 May;37(4):425-35.

Bocci, Toxicol Appl Pharmacol. 2006 Nov 1;216(3):493-504. Epub 2006 Jun 27.

In this section manuscripts from Bocci were referenced 9 times. Bocci manuscripts from 1996 to 2009 were cites. None of the supposed copy references were used, and then were not cited. Dr. Velio Bocci, even when we have no doubts about his scientific abilities, is a real example of the phenomena of self-plagiarism. Short looks to his recent reviews show a recycle of information with different titles and short new ideas. That is why it is very difficult to identify the sources of the topic selected by us, but correspond to the references cited properly.

Those pages none only include cited of Bocci, we use our own references:

Al-Dalain, Martinez-Sanchez et al. 2001

Martinez-Sanchez et al. 2005

The fragment highlighted is not identically to the original sources, was up-date; unit was homogenate to $\mu\text{g/mL}$; concentration of O₃ and blood volume were established according our experience and previous papers.

6. Page 42 /43 is supposed to be copied from:

Niki E. Free Radic Biol Med. 2009 Sep 1;47(5):469-84. Epub 2009 Jun 24.

Ideas expressed by Niki (2009) were cited three times in this fragment, because the discussion in this case was focused in a topic in which the author is devoted, but are properly cited:

[....] physically and emotionally (Niki 2009). [....]

[....] level of oxidative damage and diseases (Niki 2009). [....]

[....] responses above 1 μ M (Niki 2009). [....]

In addition, included citation and ideas supported by others: Renn 2008, Noguchi 2008, Sultana et al. 2006, Blair 2008, Pratico 2008 and Piga et al. 2007, Gutierrez et al. 2006, Ishikawa et al. 1997 and finally also Bocci 2005.

8. Page 44 /45 is supposed to be copied from:

Valacchi G, Fortino V, Bocci V. Br J Dermatol. 2005 Dec;153(6):1096-100.

Certainly, in the topic addressed in this section Valacchi is, without any doubts, an expert. That is why his manuscripts (3 references, cited 5 times) were cited.

[....] concentrations can have useful effects (Valacchi et al. 2005) [....]

[....] oil to chronic wounds (Valacchi et al. 2005). [....]

[....] blot and immunohistochemical analysis (Valacchi et al. 2002). [....]

[....] in cutaneous tissues (Valacchi et al. 2003). [....]

[....] exposure (0.8 μ g/g for 6 h/day) (Valacchi et al. 2004). [....]

In addition, including citation and ideas supported by others: Thiele et al. 1997a, Thiele et al. 1997b, Thiele et al. 2001, Sato et al. 2001, Bocci 2005 and Calabrese 2008.

Conclusion

The review in *Dose Response* (2011) wrote by Martinez-Sánchez, Re et al. fits the concept of *analytical review*. It was a review of 77 references from 1992 to 2009 to summarized and update the main elements concerning to the applicability of hormesis concept in ozone therapy. By the first time, was associated the behavior of ozone in therapy with the *hormetin* concept. In addition, original Fig. 1 and 2 hypothesized and summarized the explanation addressed in the text body.

Reference:

1. Re L. La Terapia con Ossigeno Ozono o Ozormesi: recenti acquisizioni scientifiche. Bollettino dell'Ordine dei Medici della Provincia di Ancona Medici & Medici. 2008;16:18-20.
2. Leon OS, Menendez S, Merino N, et al. Ozone oxidative preconditioning: a protection against cellular damage by free radicals. Mediators Inflamm. 1998;7(4):289-94.
3. Bocci VA, Zanardi I, Travagli V. Ozone acting on human blood yields a hormetic dose-response relationship. J Transl Med. 2011 May 17;9(1):66.
4. Day R, B. G. How to Write and Publish a Scientific Paper. 6 ed: Greenwood; 2006.
5. Bocci V. Oxygen-Ozone therapy. A critical evaluation: The Netherlands: Kluwer Academic Publishers; 2002. 440 p.
6. Bocci V. Is it true that ozone is always toxic? The end of a dogma. Toxicol Appl Pharmacol. 2006 Nov 1;216(3):493-504.
7. Ross J, Hu L. Septic arthritis of the pubic symphysis: Review of 100 Cases. Medicine. 2003;82(5):340-5.