

To  
Professor Radha K Dhiman  
Editor in Chief  
Journal of Clinical and Experimental Hepatology

&

Sameer Gupta  
Publisher, STMJ - IJPP – India

From  
Dr Cyriac Abby Philips  
Chief Consultant, The Liver Unit  
Cochin Gastroenterology Group  
Ernakulam Medical Center  
Kochi, Kerala, India

Subject: Reply to Dr Steven Newmaster, Director, NHP Research Alliance on Philips, **Cyriac A. et al. 2018. Slimming to the Death: Herbalife®-Associated Fatal Acute Liver Failure—Heavy Metals, Toxic Compounds, Bacterial Contaminants and Psychotropic Agents in Products Sold in India. Journal of Clinical and Experimental Hepatology, Volume 9, Issue 2, 268 – 272** – Regarding

Dear Sir

We would like to submit our response to criticisms raised by one Dr Steven Newmaster, PhD (Botany) regarding our recently published manuscript in the peer reviewed official journal of The Indian National Association for the Study of Liver, Journal of Clinical and Experimental Hepatology (JCEH) published by Elsevier.

Dr Steven Newmaster has requested that the published manuscript be retracted in the light of poor science, bogus claims and fraudulent use of data. We disagree with him in all of these aspects. Dr Steven has also challenged the peer review process of Elsevier and JCEH and directly and indirectly insulted the peer-reviewers by providing a better review of the published manuscript which has been extensively evaluated by him and his scientific team. Before we go on to the detailed explanations that will provide reasonable and scientific answers to Dr Steven's queries, we would like the Editorial Board and the Journal to kindly make note of the following facts regarding Dr Steven and his scientific team.

- Dr Steven Newmaster is the Botanical Director at the Biodiversity Institute of Ontario (BIO) and Associate Professor of Integrative Biology at the University of Guelph. His research specializes in plant diversity and identification systems including DNA barcoding and has publications on biodiversity genomics including: DNA barcoding, medicinal plants, ethnobotany genomics, new species discovery, plant classification, and ecosystem management. He lectures on botany, biodiversity genomics, ethnobiology and conservation biology.
- Dr Subramanyam Ragupathy is the Chief Curator of BIO Herbarium at the University of Guelph, Department of Integrative Biology.
- Dr Dhivya Shanmughanandhan currently holds the post-doc position in botanical research at the University of Guelph.

- Dr Prasad Kesanakurti is a research scientist at the University of Guelph, Centre for Biodiversity Genomics
- Dr Hanan Shehata holds the position of post-doctoral fellow in the Department of Integrative Biology at University of Guelph
- Dr Thirugnanasambandam (Thiru) Arunachalam is a research scientist in the Department of Structural and Computational Biology (Crystallography, NMR and Drug development) and Metabologenomics at the University of Guelph.

With all due respect to these scientists who are experts in their own fields, **NONE** of the members of the scientific review team including Dr Steven Newmaster have **ABSOLUTELY NO** experience in diagnosing, treating and managing drug induced liver injury, acute liver failure and the whole team **LACKS** the required basic and translational scientific acumen in Hepatology to review our published article on drug induced liver injury and acute liver failure. Ideally, peer review and constructive criticisms **MUST BE** provided from experts in the same field on which the manuscript is based on. JCEH and Elsevier **HAS EXACTLY done** what every proper peer review must follow through and there remains no doubts that the peer review was pristine. Directly asking for retraction of the published manuscript, **by 'EXPERTS' in** Botany, Genetics and Crystallography (most of whom are still holding fellow positions and are students) is an insult to the journal, its peer review and the editorial board. For example, we do not expect a gardener to provide insights on how Satellite-Communications work. We also do not expect an Ophthalmologist to provide criticisms or insights on a 24-week pregnant woman with jaundice and ascites. I hope these examples shed light on how we are on different pages. However, taking into consideration, the time spent by Dr Steven and his team to painstakingly go through each and every line of our published article and also taking into consideration, they are fellow scientists, we, as authors of the published manuscript are willing to provide absolute and reasonable answers to all **SCIENTIFIC** queries raised by Steven et al knowing well, the fact, they have absolutely no experience in making such criticism, we are willing to provide detailed answers, so that this may be a learning experience for Dr Steven and his Scientific Review Team. All **LAY QUERIES WILL** be marked with a **§** sign and befitting replies will be provided, but will not be considered for further discussion. At the end of our discussion, we will tally the **LAY and REASONABLE SCIENTIFIC QUERIES** so as to provide a clear picture to conclude that the published work is authentic, scientific and **MUST NOT BE RETRACTED** because we stand with science, patient and public health and most importantly, health education which becomes **the CORE of our published work.**

We also notify the Publisher and the JCEH Editor in Chief and the Editorial Board that Dr Steven Newmaster serves THE NHP ALLIANCE which is based at the University of Guelph (a private institute) and is an initiative that aims to develop new, mutually agreed upon standards for botanical species ingredient authentication. Herbalife Nutrition, whose products feature in the published article on acute liver failure in the JCEH, is a member and **SPONSOR** of the Alliance, the latter which engages in DNA-based tools to ensure Herbalife nutrition products consist of the exact species of plants and botanicals needed to support the company's products' health claims. Please note the following points in this regard:

1. Dr Newmaster, the Director of NHP, is directly or indirectly working/employed with Herbalife Nutrition. Herbalife Nutrition has stated that they 'are proud to be a Sponsor and member of the Alliance'. This means that NHP Alliance receives funds in the form of sponsorship from Herbalife Nutrition (figures below):

toolset used to ensure consumers have access to authentic products.

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## Herbalife

Herbalife Nutrition has been developing the science around our botanical ingredients and products for many years, focusing on transparency and accountability. The relationship we established with the University of Guelph and the Natural Health Products Research Alliance will help develop new, mutually agreed upon standards for the industry that will directly benefit the consumer. We are proud to be a Sponsor and member of the Alliance.

[Visit Partner Website >](#)

## TRU-ID

A founding platinum sponsor of the NHP Alliance that embraces cutting edge molecular diagnostic methods within a standard for authentication of ingredients as a consumer facing certification mark. Over 30 million NHP products are now TRU-ID certified with the help of the NHP Research Alliance!

## Herbalife

Herbalife Nutrition, a gold member, has been developing the science around our botanical ingredients and products for many years, focusing on transparency and accountability. The relationship we established with the University of Guelph and the Natural Health Products Research Alliance will help develop new, mutually agreed upon standards for the industry that will directly benefit the consumer.

**We are proud to be a Sponsor and member of the Alliance.**

## Nature's Way

Nature's Way is excited to be a part of the NHP Research Alliance as a gold member, allowing important access to the University of Guelph, a global research leader in biogenomics and food science. This is an opportunity for the dietary supplement and NHP industry to influence molecular diagnostic research that will expand the quality control toolset used to ensure consumers have access to authentic products.

2. Dr Newmaster **HAS NOT MADE THIS DISCLOSURE IN HIS REVIEW** and **HAS FAILED TO DISCLOSE A POTENTIALLY MAJOR CONFLICT OF INTEREST** to the Journal, the Editor in Chief and the Publisher. This is very shameful and of shows only **VESTED MONETARY or NON-MONETARY INTERESTS** that lie with Dr Newmaster and his scientific team. In the pretext of 'poor science' and 'bogus fraudulent data claims', Dr Newmaster has belittled science, shamed clinical scientists such as the authors of the published manuscript, insulted a peer

reviewed well renowned journal and a reputable Publisher. This is an offence and should be dealt with, through proper channel.

**In the letter below, Dr Newmaster ONLY speaks about saving 'THE STAKEHOLDERS' of which NHP ALLIANCE, of which, Dr Stevens is the Director, belongs to. Hence, in the name of FAKE scientific invalidity and wrong accusations, Dr Stevens, on behalf of Herbalife Nutrition is trying to 'bury the hatchet' by targeting reputable clinicians, clinical scientists and Journal/Publisher.**

**From:** Steven Newmaster <[snewmast@uoguelph.ca](mailto:snewmast@uoguelph.ca)>

**Sent:** Friday, May 24, 2019 4:00 AM

**To:** Gupta, Sameer (ELS-DEL)

**Cc:** [kpsdhiran@hotmail.com](mailto:kpsdhiran@hotmail.com); Boniface, Adeitia K. (ELS-CHN); Journal of Clinical and Experimental Hepatology; Subramanyam Ragupathy; Dhivya Shanmughanandhan; Hanan Shehata; Prasad Kesanakurti; Thiru Arunachalam

**Subject:** Re: Editor contact email requested [190513-012502]

Dear Sameer,

Thank you for your immediate response. Given the negative publicity and damage to this market sector from this article, I expect this will be dealt with promptly before more measurable damage occurs amongst the stakeholders. I look forward to the collective response from your editorial team.

Sincerely,

Steven

**Dr Steven Newmaster**

Director, NHP Research Alliance

Professor, IB/CBS,

BIO CBG 208, University of Guelph

Guelph Ontario, N1G4T2

Iphone: 519-993-8467

3. Dr Newmaster and The NHP Alliance only performs ingredient science research and identification of new botanicals for Herbalife usage. He and the team at NHP **DOES NOT PERFORM / HAS NO DATA / DO NOT OVERSEE** the safety and efficacy of herbal and dietary supplements marketed by Herbalife Nutrition and **DOES NOT PERFORM POST MARKETING SURVEILLANCE of these products** which is one of the core educational tip of our published manuscript.
4. Please note the box-marked statements in the paragraphs of the covering letter sent by Dr Stevens to the Journal Publisher below:



The review process for the Philips et al. 2018 publication failed to follow the outline suggested by Elsevier entitled “Reviewing scientific manuscripts: A comprehensive guide for peer reviewers” (Brown et al. 2017, <https://doi.org/10.1016/j.jtcvs.2016.12.067>). We have provided comprehensive review following these criteria, of which we would recommend rejection of the Philip’s manuscript for publication as it has major flaws and fails to address most of the criteria listed in this Journal’s guidelines for acceptable publication. There is an ethical requirement for scientists to build knowledge following scientific method based on data, correct analyses and interpretation of that data. The Philips et al. manuscript is largely not factual, nor based on scientific method, which results in the communication of damaging, unsubstantiated claims to stakeholders within society at large. This undermines the scientific process, discredits scientists and damages multiple industry stakeholders.

We have made several requests below to see methodologies, data, statistical and bioinformatic analyses needed to support the claims made in this manuscript. We hope the authors and journal editors will respect this request in support of following proper scientific method. This does not negate our request to have this article retracted immediately as I have heard from many colleagues who are documenting the negative fallout from this manuscript that has created false news, which we will correct. We are all very disappointed that the scientific review process has failed in allowing this manuscript to be published.

- In these sentences, it is very clear that there is definitely ‘monetary losses’ to the person who prepared this letter and his ‘colleagues’. They fail to see the real fallout, which is education regarding potential toxicities of herbal and dietary supplements on public health and the growth of a misinformed general as well as patient population.

Attached is a detailed review of the Philips et al. article, which clearly underpins our concerns and request to have this article retracted immediately. Our review is meant to uphold the integrity of this Elsevier journal by identifying invalid research in order to maintain the quality of the journal. We have an ethical obligation to the research community and relevant stakeholders to ensure the publication of accurate, scientifically valid knowledge. The collective knowledge from our research team (see below) represents over 200 journal publications and decades of experience within this subject area that can help prevent ethical breaches by identifying unsubstantiated claims and research fraud.

- Please note that the above statement **is FALSE** and Dr Stevens or his team, even though rich in experience and publications in the field of Botany and Genetics, **have ABSOLUTELY NO PUBLICATIONS/AND HAVE NO EXPERIENCE** to review and criticise on Clinical and Translational Hepatology, Hepatology related Pathology, Drug Induced Liver Injury and Acute Liver Failure which form the core of our published manuscript.
- Kindly note that the senior author of the published manuscript (Dr PA) has 4 decades of experience in treating liver disease patients and is one of the founding fathers of Gastroenterology in India. The first author and corresponding author (Dr CAP) has > 130 publications in peer reviewed journal on liver diseases including the New England Journal of

Medicine, Hepatology and Journal of Hepatology, JCEH and IJG, and is a multi-award-winning clinician scientist based on his work on liver diseases.

Dr Steven Newmaster's review of our published manuscript is soaked in threat, developed on bias and written with dissent, in the absence of any appreciable clinical acumen or constructive criticism that is required of a 'good' scientific review. Furthermore, Dr Steven Newmaster chooses his words very poorly and forms sentences that directly and personally attack the reputation of the authors of the published manuscript as well the Journal and mocks the peer review without any concern for fellow scientists. This cannot be tolerated and will not be. We are not bound to answer a 'lay person' who is a 'self-proclaimed expert' in the field of Hepatology, with regards to our manuscript which has already been peer reviewed, but we chose to do so only to defend the Journal and to douse the poison that Dr Steven Newmaster has spewed onto us and our scientific work. Our response also means that we truly stand up for science and our patients and we will continue to do so in the future. Our patient's report is worthy of staying on because it is scientifically sound and ethically valid and it brings in health education efforts to improve public health. The authors interest in this manuscript is only patient centred, while Dr Newmaster's interest in retracting the article is centred on vested interests that lie with his NHP Alliance who are sponsored by Herbalife Nutrition.

After extensively reviewing Dr Steven's report and providing reasonable answers to his queries we come to the following conclusion:

- a. >80% of the queries are marked with **\$** which means that more > 80% of accusations and 'scientific review' made by Dr Steven and his team are of poor quality, utilizing lay terms, quoting invalid references and biased in conclusions. Only approximately 20% of the queries were valid to which we could provide proper responses. Dr Steven has also ushered in much of his 'technical' expertise to forcefully and falsely allege improper scientific technical utilization in our study, when in fact, our study methodologies are pristine, credible, based on published standards and strong in conclusions. A large proportion of the technical discussion put forth by Dr Steven does not relate to our study and cannot be considered for further parley.
- b. Only 2 points raised by Dr Steven is valid in review of our manuscript. One, an erroneously marked magnification in the Figure 1 and an erroneously mentioned heavy metal symbol for Thallium (Th instead of TI). These two points DO NOT amount to retraction of the manuscript, since all of the rest of the points raised by Dr Steven are either lay comments without substance and scientific value OR are scientific comments to which we have provided very sensible and reasonable answers to.

**Taking into consideration the following facts we strongly argue that our published work DOES NOT fall into any of the categories for retraction and that it needs to remain where it is meant to be, for 'all' to read, learn and understand.**

- a. Dr Steven Newmaster is directly or indirectly employed by Herbalife Nutrition.
- b. Dr Steven Newmaster failed to disclose his association with Herbalife and did not provide conflict of interest statements
- c. Dr Steven Newmaster is the Director of the organization NHP Alliance which is sponsored by Herbalife Nutrition
- d. Dr Steven Newmaster does not have any concern for public health or patient outcomes and has only, on multiple occasions, very strongly spoken about/for the 'stakeholders' and 'monetary losses' associated with Herbalife, all in the pretext of describing falsely, our peer reviewed publication and directly insulted the Journal, the Editorial Board and the Publisher.

- e. Dr Steven Newmaster and his scientific team ARE NOT experts in the field of medicine, internal medicine, hepatology and liver pathology and has no published or other experience in these. His scientific review team comprised of 'plant scientists' who are not authorized to perform clinical reviews.
- f. Dr Steven and his team fail miserably in providing satisfactory defence to our scientifically strong published work and quote invalid references and outdated data from literature. Dr Steven keeps repeating the same mistakes over and over in his discussions which makes reading through the review feel like a 'repetitive outburst of frustration' that personally targets reputed authors and clinical scientists without scientific acumen.
- g. There are no formidable statements from Dr Steven that portray our publication in the wrong. All his statements have been well defended wherever applicable with science and the internet is rich with acceptance of our article and is one of the most socially relevant articles published by Elsevier that received world wide attention and has been the most important article to be discussed from Elsevier from the Asia Pacific region, the world over (<https://plu.mx/plum/a/?doi=10.1016/j.jceh.2018.08.002&theme=plum-jbs-theme&hideUsage=true>)
- h. Dr Steven has asked for confidential patient data without even understanding protocols for the same. Even though a published scientist himself, he does not care for patient confidentiality, patient outcome and does not follow protocol. This shows paucity in clinical acumen and lack of expertise to comment on our manuscript. Hence, all comments made by Dr Steven are in fact, to be taken as lay comments.
- i. As authors of the manuscript, we are willing to share raw data sets, patient biopsy slides and blocks and the surviving patient family detail to the JCEH Editor in Chief and Editorial Board and the Publisher if they wish to see such detail. We are also willing to share details of the receipts of Herbalife products we acquired for analysis. The products themselves are not present anymore since they perished and rotted away and we had to discard them (stored for almost 6 months in a fridge facility).

Last, but not the least, we bring to kind attention, of the Editor in Chief, The Journal Editorial Board and The Publisher Elsevier, that **NOT A SINGLE MANUSCRIPT PUBLISHED ON HERBALIFE IN LITERATURE HAS EVER BEEN RETRACTED** which speaks for the authenticity of our work and echoes the collective, thorough scientific conclusion, that every clinician who has published in this regard, has made on these products in published literature.

We hope our responses have been adequate and reasonable and this matter remain closed for further discussion since we do not have the time, from our patient care activities, to make responses to lay queries from Dr Steven Newmaster et al anymore, but are willing to share further raw data with the Journal and Peer Review should they wish to review.

Thanking you  
Kind regards

Dr Cyriac Abby Philips  
Dr Philip Augustine  
Dr S Rajesh  
Dr Gopakumar C Valiathan  
Dr Solomon K John

- On behalf of The Liver Unit, Cochin Gastroenterology Group, EMC Hospital, Kochi, Kerala, India

## In the next sections we come to the detailed answers to queries raised by Dr Stevens et al.

The queries are provided as screen shots and the answers feature beneath the screen shot specific to the bullet points.

### §

**Title:** “Slimming to the Death: Herbalife®-Associated Fatal Acute Liver Failure—Heavy Metals, Toxic Compounds, Bacterial Contaminants and Psychotropic Agents in Products Sold in India”

- Inappropriate title with unprofessional bias and tone for a scientific Journal.
- Unsupported claim. Underlined sections not supported by research/data provided in the body of the research article. See comments below in our critical review below.
- The title is factual. There is no bias or unprofessionalism intended. Factual titles are considered adequate for case reports. A more scientific title would be better suited for a randomized controlled trial which this report is not.
- The underlined sentences ARE IN FACT supported well by our clinical diagnosis, analysis and discussion. We invite Dr Stevens et al to read through our published manuscript with sincere attentiveness.

### §

#### **Abstract:**

“Herbalife is a global nutrition and weight management company selling and marketing nutritional and weight loss supplements. The United States Federal Trade Commission described Herbalife in 2016 as a scam disguised as healthy living. Herbalife-associated liver injury was reported from multiple countries in the West. India is fast becoming the largest growing market for Herbalife products, expected to surpass the United States in sales revenue”.

- The abstract is not written for a professional scientific journal, but rather a business/news article written with an inappropriate tone and unsupported accusations.
- There appears to be a bias by the authors aiming to discredit an industry and manufacturer. This is not appropriate use of scientific writing.
- The following claims are not supported as defined in the abstract.
- The abstract has to start with an introduction which is based on data already published in literature which we have only echoed. This is not a legal notice paper, but a published peer reviewed manuscript. The usage of ‘accusation’ is not befitting a ‘scientific peer review’ team headed by a senior scientist. There is no bias in reporting and all claims are well supported including patient detail, outcomes and conclusions. These are lay comments from Stevens et al.

### §

“We report the first case of a fatal acute liver failure from the Asia-Pacific region, in a young woman who consumed Herbalife\_ products over 2 months.”

- Cannot make claim based on the data presented.
- This is misleading and incorrect assumptions based on bogus interpretation of the data.
- Lay comments from Dr Steven et al. This is in fact the first case on Herbalife associated fatal ALF from Asia-Pacific region. We suggest the scientific team do a better search on published



data on the same. Kindly refrain from using derogatory and colloquial terms such as 'bogus' in a scientific discussion.

§

“We also present unsettling data that showcase heavy metal contamination, toxic compounds, psychotropic substances, and pathogenic bacterial contamination in similar Herbalife\_ products in India. The growth of Herbalife\_ in India and expansion of its nutrition clubs in major cities that promise fake health benefits portend a serious public health concern.”

- There is No data to support any of these claims.
- These are bogus claims because they are not based on scientific method, hypotheses and statistical analysis. This is misuse of scientific publications and is not ethical.
- Lay comments similar to above. Final statement based on report conclusion is valid.

**Introduction:**

“Well-described large **studies** have shown that various HDSs are associated with severe liver injury.<sup>1</sup>

- No support for this claim and inappropriate/misleading use of a reference. The authors have mentioned “Well-described large studies” in the first paragraph and have quoted only one reference that is not a large study.
- Poorly developed introduction with little structure.
- Lack of proper reference to back ground literature – large bodies of literature have been ignored while others are not cited correctly, which is an evidence of authors bias, which is not professional.
- No project goal, questions or experimental design at the end of the introduction as should be expected. What is the objective of this paper? Study? Research project?
- We have quoted the most recent review that mentions every study done on HDS. Steven et al has obviously not gone through the whole article in references and we suggest they do so before making statements that sound scientifically lame. The US DILIN network has published the largest series on HDS in the world and we invite Steven et al to go through the same.
- Statements at bullet points 2, 3 are lay comments without any strong references from Steven et al. We request them to concentrate on scientific criticism and constructive detail.
- Dr Steven and colleagues who performed ‘critical review’ of our manuscript may kindly study the Author Guidelines as to how a Case Report is written. They are also welcome to go through any case report published in the journal to get a proper idea of the same. Aims, Objectives, End points, study design and ‘projects’ all form part of clinical trials and mostly randomized controlled trials or large observational or longitudinal prospective studies. It is very clear and evident from these statements by Dr Steven that knowledge regarding proper research methodology in various forms of scientific writing is completely lacking in the scientific team that conducted this ‘repeat peer review’.

## §

### CASE REPORT

“A 24-year-old woman with hypothyroidism without other chronic illnesses, on thyroxine supplementation in the last 5 years (75mcg once daily)”

- What is the medical history of the patient? There are reports of liver damage and deaths based on the long-term use of the medications prescribed for hypothyroidism (see Ref 1 and 2), unfortunately in this paper there is no proper monitoring/tracking of the thyroid hormone levels in the patient. There are many alternative explanations for liver damage that were not investigated or discussed. I would expect clever hypotheses from medical researchers, yet there is no intellectual design for this study, which is disappointing.
- Hypothyroidism leading to hyperlipidemia and obesity can cause nonalcoholic steatohepatitis, cirrhosis or liver cancer. One of many explanations never discussed.

“A 24-year-old woman with hypothyroidism without other chronic illnesses, on thyroxine supplementation in the last 5 years (75mcg once daily), with a body mass index of 32.1

- A previous study reported that hypothyroidism patients were more likely to have nonalcoholic fatty liver disease and nonalcoholic steatohepatitis (see Ref 3).
- Medication for hypothyroidism is thyroxine supplementation. Long term supplementation with thyroxine has never been reported to cause acute liver failure. Dr Steven has completely missed the point, quoted a review article on hypothyroidism physiology and erroneously stated that hypothyroidism medications can cause liver failure **when IN FACT**, it is drugs used for hyperthyroidism that has been shown to cause acute liver injury. Our patient was not on hyperthyroid medication, but on thyroxine supplements in **VERY LOW DOSES** that has never shown to cause liver injury, leave alone acute liver failure.
- NASH never causes acute liver failure (not reported in literature), we ruled out cirrhosis and cancer on imaging and liver biopsy. We are discussing a patient of acute liver failure and Dr Steven has proven the fact that he and his scientific team does not even realize what the disease in discussion is about.
- Hypothyroidism patients have steatohepatitis. Our patient had steatosis on biopsy which we agree to and have mentioned in the biopsy discussion. This does not cause acute liver failure. May be in patients with steatosis and steatohepatitis, Herbalife potentiates acute liver injury leading to acute liver failure. Can Dr Stevens and his scientific team provide published data that Herbalife does not?

## §

“with a body mass index of 32.1 was initiated on three Herbalife slimming products (Formula 1 Shake Mix, two scoops twice daily with skimmed milk; Personalized Protein Powder, two tablespoons into the Shake Mix twice daily and Afresh Energy Drink, 10 g twice daily)”

- A patient with the history of Thyroid problem is usually not recommended to consume high levels of protein; neither plant-based nor animal-based protein. Without physician's recommendation, altering one's diet may cause serious effects. It is not clear from the case report if the patient had taken advice from her doctor for consuming protein powder during her conventional medical treatment. It would be good to know what the unregistered nutritional club recommended.
- The patient consumed Herbalife supplements as per advice of a Herbalife Associate running a nutritional club in the locality where she belonged to. Her husband was the person who brought the supplements. The history and the sequence of events after consumption of the products has been provided by the husband and the patient's sister. This is not a joke and Dr Stevens must realize that a life was lost. The first sentence in the above screenshot is substantiated with very poor references. This is a very poorly constructed argument from Dr

Steven and team without proper references to back up the statement on avoidance of protein in hypothyroid patients. A physician does not alter one's diet, but a registered and trained dietician does so, based on physician's inputs. What is a registered nutritional Club? Does registration mean Government registration, or only Herbalife registration? Any centre that provides food products / supplements as part of weight loss in patients with comorbidities need specific regulatory approval from the Government health agencies in the specified locality. Does Dr Steven et al keep a tab on all registered Herbalife nutrition clubs? How much data does Dr Stevens have on nutrition clubs in Kerala, India? How much post marketing surveillance do Dr Stevens have on Herbalife products in registered nutritional clubs in Kerala, India? They may kindly share this data to understand what clubs recommend the patients based on regional differences in diet and chronic illnesses. What the club recommended is described in detail in the manuscript. We invite Dr Stevens et al to read through our published manuscript with sincere attentiveness.

## §

- Key reference missing that refutes the authors statement – Ref 26: Palkowska-Goździk, E., Lachowicz, K., & Rosolowska-Huszcz, D. (2018). Effects of dietary protein on thyroid axis activity. *Nutrients*, 10(1), 5.
- It is unclear why the authors have tried to develop hypotheses or conceptualize what may have caused the death of the 24 year old girl. The premise of a basic principle of "Protein intake by a patient with thyroid problem" itself creates more health issues and leads to higher degree of complexity in the experimental model needed to define the cause of death. There is no evidence to support the authors accusation that Herbalife products caused the death of this girl is outrageous and suggests the authors have biased views, which is inappropriate in science and unethical as it undermines the scientific process of publication, which should filter out any form of scientific bias leading to bogus claims.
- This key reference is not valid as it does not provide data on acute liver failure
- Protein intake by a hypothyroid patient leading to acute liver failure is Dr Stevens hypothesis and not ours. For us, in black and white, the acute liver failure was due to the HDS consumed since we ruled out all other known causes for the same as per defined set of clinical protocols for causality.

## §

"The patient was not on any other medications or complementary and alternative drugs before or during this time".

- This is contrary to what authors mentioned in the beginning of the paragraph. Earlier they mentioned that patient was on thyroxine supplementation in the last 5 years and now they claim the patient was not on any other medications before or during this time. Also, it is not clear if patient used thyroxine supplementation during the two-month period of Herbalife product consumption. If patient did not use thyroxine during this time (as authors reported) this should have exacerbated, her condition of hypothyroidism and affected her overall health. This is a confusing contradiction given the authors background in medicine – many glaring errors and contradictions such as this are reported throughout the manuscript.
- Please read well and carefully. Was not on 'any other' which means we have already discussed regarding thyroxine supplementation. Such lay comments are not welcome from a 'scientific team'. Thyroxine does not exacerbate, but ameliorates hypothyroidism. We suggest Dr Steven and his team learn basics of clinical medicine or ask advice from clinical scientists before preparing long paragraphs which they feel are valid, but in fact, is quite the opposite.

In the last line of the paragraph screenshot above – we politely suggest that Dr Stevens do not insult the clinical scientist authors behind this important published work. These are only **PERSONAL ATTACKS and CHARACTER ASSASSINATION** based on flawed statements from Dr Stevens. This is taken very seriously and such comments in the future will be dealt with in strong justified manner.

## §

### Page 2-Column-2

“We also sourced similar Herbalife products from the internet (total of 8 samples) and subjected them to heavy metal analysis (inductively coupled plasma optical emission spectrometry [Agilent Technologies, Santa Clara, California, USA]) and toxicology (triple quadrupole gas chromatography and dual mass spectroscopy [Thermo Fisher Scientific, Waltham, Massachusetts, USA]) and bacterial contamination studies using 16s RNA metagenomics (Illumina MiSeq next-generation sequencer [Illumina, California, USA]);”

- “Similar products” is poor experiment as it introduces a huge source of variability that is not directly comparable. This is not an acceptable design for cause and effect claims.
- Lack of sampling: Testing only 8 samples and associating the results to that of a patient's death is not acceptable. More extensive testing by including a larger number of samples is needed in order to support the claims made by the authors. There are statistical methods for determining sample size of which the authors fail to report or reference. This must be provided for the reviewers to evaluate whether or not the sample size is large enough to prevent false negative or positive results and subsequent claims.
- No references for the described techniques are found. Not sure how this manuscript made it through publication without these details. We request these details.
- No description of the methodology of each of the techniques are found, which violates a basic premise of scientific method – it must be repeatable/reproducible science. We request to see the methods and the raw data for analysis of quality and accuracy.
- Similar product as in the EXACT same branded product. Please read in context and the meaning will become reasonable.
- Sample size calculation is not required for case reports. Dr Stevens is providing very poorly made claims and trying very hard to find faults with the publication. A matter in which he fails miserably.
- The last point is a direct attack and insult to peer review and Editorial Board of JCEH and an intended shaming of the publisher, Elsevier. All techniques and methods have been described as per standard guidelines for testing, which is already published. Please see page 269 of the published manuscript last paragraph for the standardized technology that we utilized. There is no requirement for discussing these in a case report unless peer review warrants the detail. But if Dr Steven and colleagues would like to know, here are the published and standardized links for methodology which we utilized in our study.
  - i. <http://hpst.cz/sites/default/files/attachments/icp-oes-5991-8147en-ebook.pdf>
  - ii. <https://www.thermofisher.com/order/catalog/product/TSQ9K-VPI>
  - iii. [https://support.illumina.com/documents/documentation/chemistry\\_documentation/16s/16s-metagenomic-library-prep-guide-15044223-b.pdf](https://support.illumina.com/documents/documentation/chemistry_documentation/16s/16s-metagenomic-library-prep-guide-15044223-b.pdf)
  - iv. <http://qiime.org/>
  - v. [http://qiime.org/home\\_static/dataFiles.html](http://qiime.org/home_static/dataFiles.html)
  - vi. <http://www.tiem.utk.edu/~gross/bioed/bealsmodules/shannonDI.html>

There have been no new methods utilized for us to describe everything in a case report. A case report has word limits and we must describe and discuss that which is most salient. We are unsure if Dr Stevens realize how a case report is written/stylized?

- Methodology descriptions are already known and standardized based on the technology and software utilized which is repeatable and reproducible and highly quoted in literature. Please see above for more details (links provided).

**Figure 1:**

- The scale is indicated as 20X on figures 1 C and D. This does not seem to be true. Figure 1C seems to be 400X. No scale was mentioned for figure 1A and 1B.
- It not possible to identify periportal and perivenular bridging necrosis with the magnification in figure 1D.
- There is no chain of custody or known provenance reported to link these images to tissues and ultimately a subject. This evidence must be provided in order for this figure to be included in this publication. These images could be from anywhere. We request to see this data.
- These points do not amount to retraction and does not change our clinical findings and discussions and final results. The biopsy reports are accurate. There might have been a labelling error on the magnification (we thank Dr Steven for pointing that out) which we could supplement with an erratum. As for the biopsy findings, Dr Steven or his team are not trained in liver pathology and pathology of acute liver injury and our descriptions are accurate.
- Tissues and blocks are stored in our pathology lab. Patient confidentiality is maintained for such samples. These images are of the patient herself, before her death, obtained though a transjugular liver biopsy (performed by one of the co-authors Dr SR). Dr Steven or his team do not have the authority to access this data, but we are willing to provide the tissue blocks to the Journal and the Editorial Board/ Peer Reviewers should they choose to see it. There is a minimum required decorum and set of rules to ask for patient related raw data which Dr Steven does not even know about. We suggest he learn about the same. If Dr Steven or a member of his team (and no one else) who reviewed our manuscript could travel to our centre, we will be glad to show you/team the slides after obtaining consent from the dead patient's family member. This would also be a chance for Dr Steven/or his team member to meet with the still grieving patient family and understand events first hand.

**Page 2-column 2:**

“and bacterial contamination studies using 16s RNA metagenomics (Illumina MiSeq next-generation sequencer [Illumina, California, USA]; operational units classified taxonomically according to the Greengenes Database; Shannon diversity index for description of species diversity in each bacterial community using the Quantitative Insights into Microbial Ecology).”

- No details were given on how 16s metagenomics were conducted. We request all genomic methods, data including details on bioinformatics and statistical models.
- The authors did not indicate which region of 16s was targeted, which primers were used, how sequencing data were analyzed, nor the percentage for sequence similarity when assigning operational taxonomic units to the Greengenes Database.
- The quality of the genomic data is questionable. The authors need to provide data so the readers can assess the quality of the sequence reads. This is basic information that is not provided and indicates a general lack of understanding for normal recording and publication of genomic data. This puts in question all the basic sequencing and bioinformatic analysis results that normally would be supplemental data published online. We request to see this basic molecular data including trace files in the spirit of transparency and publication of data for advancing science.
- The authors mention use of Shannon diversity index for description of species diversity in each bacterial community using the Quantitative Insights into Microbial Ecology. There is no proper description and interpretation of this species diversity index and there is no explanation for why this biodiversity index was chosen.
- The authors have described the bacterial community to genus level and not to the species level. Unfortunately, the methods used in this study prevented any further taxonomic resolution than the generic rank, which prevents any discussion and subsequent claims at the rank of species or which the authors violate throughout the manuscript – this is a MAJOR flaw in the paper and should have prevented publication.
- There does not appear to be any reference material sequences that are vouchered and of known provenance. This is a major flaw in the study and becomes more of an issue given

there are no bioinformatic methods defined. Incorrect bioinformatic methods will result in miss-match between the math algorithm used to match the unknown ingredient to the RM library. We request these algorithms and the underlining

- A key uncertainty in these methods highlights the lack of knowledge on the quantity and quality of DNA recovered from the processed ingredients; note that for processed products NGS is not fit for purpose because it is not a validated method in the literature.
- Please see one section above. The queries are similar and answers are already provided. The discussion Dr Steven makes in the paragraphs above are only technical which our technical team who performed the analysis have very strongly adhered to. These are all standardized tests and does not require long descriptions especially in a case report. It will only make for less space for pertinent discussions considering this is a case report. The discussion provided by Dr Steven has no relation to what the published report states. There is a lot of unnecessary technical discussion put into this ‘expert’ review that completely miss the point of the study.

### **First paragraph and figure 2:**

“On microbial analysis, bacterial deoxyribonucleic acid was isolated from 63% of samples. 16s RNA analysis revealed multiple bacterial communities, including highly pathogenic species (Figure 2), in Herbalife products.”

- There was no mention of DNA extraction protocol used. We request this information.
- No explanation for why only 5 samples were tested. There are methods for determining sample size based on haplotype diversity. Was this method used? If so, the reader needs this information to determine if enough samples were tested to answer the research questions; unfortunately, there are no research questions defined either!
- Figure 2 does not show any highly pathogenic species. In fact, it is not showing any bacterial species. Only bacterial phyla (2A) and genera (2B) are included. Clearly there is no evidence to support claims related to pathogenic species.
- The figure legend states that figure 2A shows “top 5% of significantly detected bacterial families”, however, what is shown is bacterial phyla. Moreover, no reason was mentioned for picking only top 5% of bacterial families, which is unorthodox – reader needs to know why the authors picked this cutoff level to sample taxa.
- Interference of plant plastid and mitochondria when studying bacterial communities in plants or plant products using 16S gene is very common. The authors did not mention how they solved this problem or how they filtered operational taxonomic units belonging to plant organelles and how this might have affected the bacterial diversity.
- Please see two sections above. All protocols are based on standardized techniques. These points are invalid in the context of the study and Dr Steven is trying to cherry pick rather than understand the complete manuscript and its conclusions.
- Again, we would like Dr Steven to read our manuscript carefully. We have only shown figures of samples in which significant microorganisms were isolated, numbering 5. We did not claim there were pathogenic species. But genera containing pathogenic species.
- 5% cut off is based on technical review of the diversity and nature of samples utilized for metagenomic analysis as is described in literature. For a detail review, please see <http://chao.stat.nthu.edu.tw/wordpress/paper/97.pdf>. These are all known facts and need not be discussed in detail in a case report.
- We studied processed and ready to eat HDS products for human consumption. In terms of the filtering process itself, we used the filter\_taxa\_from\_otu\_table.py script command. Working according to the QIIME SOP and understanding that the biom file contains the taxonomic classification of each OTU, we used the following command: filter\_taxa\_from\_otu\_table.py -i your.biom -o your.new.biom -n o\_\_Chlorophyta,f\_\_mitochondria. Once that was done, we then filter the fasta file to drop any representative sequences that were removed from the biom file: filter\_fasta.py -f your.fasta -b your.new.biom -o your.new.fasta. We then rebuild the phylogenetic tree if we utilized the open-reference or de novo OTU picking. These are all well known methods that form part of standardized protocol and due to lack of space in discussion due to word limits in a case report, these are understandably omitted.

**Page 3 last paragraph and first 2 lines on page 4:**

“We detected pathogenic bacterial phyla (Proteobacteria and Cyanobacteria) with the potential to cause liver injury in 63% of samples analyzed, which include perilous genera such as *Escherichia*, *Klebsiella*, *Acinetobacter* and *Streptococcus*”

- This claim is not supported and the entire statement is incorrect and misleading the reader, of which defines the whole premise of the paper including the Title and Abstract. Proteobacteria and Cyanobacteria are not pathogenic bacterial phyla. Pathogenicity can't be claimed to entire phyla. Although Proteobacteria and Cyanobacteria include some pathogens, some members of both phyla are abundant in soil, and some live-in symbiotic relationship with plants. For example, a large number of nitrogen-fixing bacteria, which help legumes with nitrogen fixation such as *Rhizobia*, commonly associated with

leguminous plants, belong to Proteobacteria (Ref 4 and 5). Similarly, some members of Cyanobacteria (*Nostoc* and *Anabaena*) can fix nitrogen (Ref 6 and 7). This may explain the presence of their DNA in the tested products which contain soybean and other plant products.

- Similarly, it is inaccurate to describe entire genera as pathogenic, since some species within a genus can be pathogenic while others are not. In fact, some members of *Escherichia*, *Klebsiella*, *Acinetobacter* and *Streptococcus* are part of the normal human microbiota (Ref 8 and 9) and/or common in soil or plant (Ref 10-13), so the authors' claim is wrong. More precisely, some species of *Acinetobacter* and *Klebsiella* were previously identified as part of the endophytic bacterial community in soybean (Ref 14), which is a component in some of the tested products.
- More importantly, no assessment of bacterial viability was conducted. NGS detects DNA even from dead cells. All the reported bacterial taxa may come from dead bacterial cells, in which case, pathogenicity claims may be irrelevant. There are tests developed to differentiate live/dead cells that should have been used.
- Major flaw in this paper is the lack of species specific and viability data and in some case strain identity could have been confirmed. None of the pathogenicity claims made in this paper are valid and based on this major flaw the paper should have been rejected for publication.
- It is unclear how authors related the patient's death to consumption of herbalife products. As mentioned earlier, if patient did not use thyroxine or any other antibiotic medication during the consumption of herbalife products this would have resulted in the worsening of her hypothyroidism and caused overgrowth of harmful bacteria in the system. There are studies that clearly established a relationship between hypothyroidism and associated bacterial overgrowth (Ref 15)
- The first point contains Dr Steven's hypothetical descriptions on the published data which we welcome, but do not add to scientific value to the patient reported outcome in discussion. The claims made in the published manuscript are highly valid when considering from the clinical point of view which Dr Steven or his team members would not understand since they do not have clinical experience or training in dealing with liver disease patients. Dr Steven is merely twisting our published facts so as to make them sound invalid. But when viewed as a whole from the clinical history to the investigations, outcome and analysis, we believe that our data is strong and very supportive of our conclusions. Dr Steven again makes wrong statements regarding thyroxine. This is just very poor scientific discussion from him and the team. They do not understand or know clinical medicine and have **ABSOLUTELY NO AUTHORITY** to make such statements about a peer reviewed published scientific report. References are quoted for the sake of quoting without even the correct clinical linkage. We are discussing bacteria in the products and Dr Steven changes the course of discussion toward bacteria in the patient. This is just absurd. There are contradictions and a frustrated approach



to find lame excuses everywhere in the manuscript without any substantiated or properly referenced or published data to these claims made by Dr Steven.

**First paragraph on page 3:**

“We found high levels of heavy metals in all the sourced Herbalife products and undisclosed toxic compounds including traces of psychotropic recreational agent in 75% of samples”

The authors referred Table1 for these results.

- No description of the methodology and references are provided for ICP-OES study. We request this information.
- Authors did not explain how the samples were prepared for ICP-OES analysis. We request this information.
- How did the authors quantify the heavy metals? What AOAC/USP method was used and what was the LOD for their methods?
- No proper reference values for the heavy metals are provided. Lack of result interpretation. We request this information.
- There is no evidence available to compare the presence of heavy metals in the patient.
- Did the authors perform any tests to detect the presence of heavy metals from the patient’s body?

- Random occurrence of heavy metals and their concentrations among the samples sourced from different places vary significantly which is evident from the results (Table 1). During the manufacturing process of Herbalife products, it is not possible to add random heavy metals to their products. See Table 1 examples below in which we have concerns:

Personalized protein powder - Thane, Maharashtra - Cd (0.19), Ba (4.75), **Cr (2.33)**, Pb (1.55), **Th (1.65)**

Personalized protein powder - Kolkata, West Bengal - Ba (5.1), **Cr (7.4)**

Personalized protein powder - Gurugram, Haryana - Cr (7), **Th (11.96)**

- For methodology that is already standardized and described, please see the sections above
- Testing heavy metals in the patient is not required to substantiate drug induced liver injury. We did not specifically mention that ONLY heavy metals caused harm. It was the HDS product which we associate with liver failure in our patient.
- How these heavy metals came in to the product is not our concern. It is the Company’s and all those who are associated with it. We can only shed light on what is wrong, the correction should be at source. This is concerning and we would like to educate the general population regarding the inhomogeneity of HDS manufacturing that would eventually help alleviate such critical patient outcomes.

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### **First column on page 4:**

The Authors mentioned the following about recreational drug:

“The presence of butyrolactones (BL) in a quarter of samples tested in our study is of great concern. Gammahydroxybutyrate and its precursors are recreational drugs of abuse. The United Nations Expert Committee on Drug Dependence stated that BL be used only for chemical industrial purposes and placed it under the Controlled Substances Act, while the US Food and Drug Administration warned on its use in food substances”

- Of all the toxic compounds listed in Table 1, only Butyrolactone seems to be considered as psychotropic drug and it (Gamma Butyrolactone) is a controlled substance in several countries. However, there are scientific reports that showed that Gamma Butyrolactone is a natural component in wines and other similar products (Ref 16 and 17). That fact that psychotropic recreational agent was found only in traces may indicate its natural occurrence rather than any motivated adulteration by Herbalife.
- Gammahydroxybutyrate is used by the bodybuilders for reducing fat and weight loss (<https://www.camh.ca/en/health-info/mental-illness-and-addiction-index/ghb>)
- We are not discussing wine and similar products. Our study is based on a different scenario.
- We are not discussing body builders. Our study is based on a different scenario.
- Presence of butyrolactones amount to adulteration or fermentation of HDS components which is also concerning regarding GMP.

### **Table 1 Critical Questions and Flaws:**

- Did the authors include appropriate standards to determine the toxic compounds?
- On what criteria, the authors had pre-chosen the standards in order to detect the toxic compounds in table 1?
- There is no evidence provided by means of figure or detailed report in the manuscript to prove that toxic compounds were present in the samples listed in table 1.
- Toxicology reporting is inaccurate: There are 7 compounds in the toxicity column (Table 1), two are potential toxins to the liver (glucosamine and hydrazine) and the other five are not direct toxins to the liver.
- There are no quantitative results given in the paper to support the claim that toxins are present at levels that are harmful; the toxicity of drugs and pathogens depends on the dosage and the mode of entry.
- Major flaw in the experimental design of this study as it fails to support key claims in the title and abstract of which are the key findings in this paper. The results stated are not sufficient to support the claims against Herbalife.
- toxicology column is a qualitative result (there is no quantitative results); toxicity of those compounds depends on the dosage.
- Yes
- As per technical descriptions on the hardware and software used
- Please see REF 7 of the published manuscript. It speaks for itself.
- Toxins can be direct or indirect. They can be metabolites also. Dr Steven does not substantiate his concerns well.
- We did not claim that the patient died due to the presence of these toxins. She died due to Herbalife consumption. Herbalife was found to have these toxins in a separate analysis. We have only shown association. Further studies from Government agencies need to be conducted as post marketing surveillance and random sampling of such products from place of sale can be done to confirm our findings.
- Toxicity can be idiosyncratic and dose independent. Dr Steven did not and cannot fully and strongly claim that every toxicity is only dose dependent.

- Hydroxy acetic acid (Glycolic acid); only toxic to liver 1000mg/Kg (potential inhibitor of O<sub>2</sub> glucose metabolism in liver (studies organism; rat) (Ref 18).
- Propenoic acid (Acrylic acid); toxic to liver at 750mg/Kg dosage (weight loss in the liver) (Ref 19).
- Cyclopropene; Toxic but, no evidence of HEPATOTOXICITY (Ref 20).
- Butyrolactone; Toxic but, no evidence of HEPATOTOXICITY (Ref 21).
- Glucosamine; possible rare cause of clinically apparent liver injury (Ref 22).
- Propene; Acute Exposure/ Inhalation exposure of Sprague-Dawley rats at concentrations of propylene up to 65000 ppm for 4 hours showed no evidence of hepatotoxicity (Ref 23).
- Hydrazine; In cases of acute human poisoning, vomiting, severe irritation of the respiratory tract with the development of pulmonary edema, central nervous system depression, and hepatic and renal damage have been reported (Ref 24).
- Please provide data in humans or, is Dr Steven very sure that rat liver toxicity studies can be extrapolated to each and every human being with and without comorbid illnesses. This discussion from Dr Steven is invalid and unsubstantiated.

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### **Table1**

#### **Herbalife Disclosed product components**

No proper literature references are quoted for the author's statement "Suspected toxic components in literature". There is no experimental data provided to suggest the presence of these suspected toxic components in the Herbalife product. No experimental validation and discussion was made on the disclosed product components of Herbalife product.

- <https://livertox.nih.gov/Herbalife.htm>
- Suspected components are well known and described and is mentioned on The Liver Tox website run by the NIH. No further strong evidence than this is required. We did not mention this as a reference due to lack of space.

## \$

**Page 3/4**

Page 3 last paragraph and first 5 lines on page 4

“We detected pathogenic bacterial phyla (Proteobacteria and Cyanobacteria) with the potential to cause liver injury in 63% of samples analysed, which include perilous genera such as Escherichia, Klebsiella, Acinetobacter and Streptococcus. **This level of microbial detection is unacceptable in processed/ vacuum packed food supplements according to the current Good Manufacturing Practices rules**”

- This is not true. GMP rules and regulations stipulate a fit for purpose validated identity test to species level resolution. The authors did not use the appropriate fit for purpose method (need species resolution), nor did they use a validated method; There are no validated AOAC methods for NGS species level testing used in this study.
- What level of microbial community (Escherichia, Klebsiella, Acinetobacter and Streptococcus) were present? This is critical information needed to understand the claim made in this text.
- Did all the samples analyzed have the same taxonomic level of microbial community?
- Did all the samples have perilous genera such as Escherichia, Klebsiella, Acinetobacter and Streptococcus? There is no evidence here to support the authors claims that underpin this article.
- Dr Stevens is working and residing in Canada. What data or regulatory rule experience does he have on GMP and HDS in India? Clearly, GMP was not well followed in the products we analysed. All methods utilized in this study are as per published literature, described protocols, peer reviewed for clarity and conciseness and hence blank statements from Dr Steven does not change any of that.
- We have defined the levels in the published manuscript. Please read through again.
- How can there be same taxonomic level? Taxonomy has different levels.
- What each sample has is already discussed in the published manuscript.

**\$**

- The authors claim that “63% of samples analysed, which include perilous genera such as Escherichia, Klebsiella, Acinetobacter and Streptococcus”. But, from figure 2B, it is evident that there is no evidence to support this claim of Klebsiella, and Escherichia presence in all the samples except sample HL-2C, in which the presence of these two bacterial community is visible. This interpretation by the authors is not correct and this is the major finding in the paper and the source of a damaging claim made to industry, which is not true. This is a serious problem for the authors.
- We did not mention all of this is present in every sample. Please go through the figure again. All discussed genera are present in the figure in specified sections. Please do not make false accusations with regard to this scientific work. This is very serious and an insult to the journal and peer review and will not be tolerated. The serious problem is not for the authors as Dr Steven might have realized. It is for unknowing patients or persons misinformed regarding such products that might land them in critical illness state.

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### **First column continuation from page 3/4:**

“This level of microbial detection is unacceptable in processed/ vacuum packed food supplements according to the current Good Manufacturing Practices rules and regulations and portends a public health threat that could lead to severe organ damage with repeated and long-term use”

- The authors have made a claim that is not tested nor supported by the data. There are many alternative explanations that need to be tested. For example, the patient was under thyroxine supplementation for 5 years, which is more relevant to long-term use. The authors have not taken this (thyroxine supplementation) or the patient’s hypothyroidic condition into consideration at all. Moreover, intake of protein powder for two months by a patient with thyroid hormone imbalance can be claimed as long-term use. The authors cannot associate the brand “Herbalife” to this unsupported claim by the authors. Consumption of any protein powder from any brand could have had the same impact on the patient.
- The authors failed to acknowledge alternative explanations – for example, it is possible that unknown toxic phytochemical constituents and adulterants from many different sources could have aggravated the liver injury in the subject patient.
- The authors have not performed any tests to confirm the possible presence of toxic phytochemical constituents and adulterants in the samples. Without evidence, the authors cannot make the assumption that the toxic phytochemical or unknown adulterants could have aggravated the liver injury in the patient. Many assumptions are made by the authors that require a very thoughtful experimental design which is lacking in this study. This is a very poorly designed study that does not have guiding objectives, questions or hypotheses to develop the experimental design. It is very disturbing to see this work published in Journal. It undermines the advancement of good science.
- The authors do not reference the extensive literature on Good Manufacturing Practices (GMP) rules and regulations that underpin quality assurance systems. These GMP regulations are strictly followed by companies such as Herbalife and enforced by regulatory agencies. How did the authors detect a serious toxic issue that is part of industry quality assurance and inspected by government regulatory Agents?
- Again, Dr Stevens makes a very, very wrong statement regarding Thyroxine and acute liver failure. Please understand that Dr Stevens critical statements are completely inaccurate and poorly substantiated.
- All the unknown toxic phytochemicals could have been component of the supplements the patient has had before she developed liver failure.
- Case report do not feature hypothesis. The observation from case reports can be utilized to prepare hypothesis for larger studies.
- What proof does Dr Steven from Canada have on GMP of HDS in India? Has he visited the manufacturing units here? Does he oversee these processes? As advocates of public health, we plan to approach State as well as Central Government Health Department to reassess GMP, product assessment and random sampling of Herbalife and other similar company products. This depends on the amount of data we can generate on HDS related toxicities which is an ongoing prospective study soon to be registered after protocol completion. We invite Dr Steven to be part of this prospective study.

### Pathway Diagram Critical Comments (Figure 2C)

- There are no methods to explain how the data was generated for this table. How did the authors perform the pathway studies? We request this information.
- What basis/criteria did the authors use to conclude that the microbiota from the sourced samples were responsible to alter functional pathways? The authors cannot make a mechanistic claim without showing how the hypotheses were developed and tested to support or refute the mechanism. I do not see any of the required science needed to make such a claim. You cannot make up mechanistic claims without scientific methods, analysis and data.
- Patients with thyroid hormone imbalance have richer microbiota than the healthy individuals. Without comparing the microbiota from the sample and the patient's body, it is impossible to claim that microbiota from the samples are responsible to alter any functional pathways. This is clearly discussed in the recent paper (see Reference 25: Zhang, J., Zhang, F., Zhao, C. et al. Endocrine (2018). <https://doi.org/10.1007/s12020-018-1831-x>).
- Figure 2c is misleading and does not support the authors claim that the microbiota from the sourced samples are responsible for altering a large number of broadly defined functional pathways. For example, the authors cannot just list a broadly defined pathway such as "Genetic information" such as "transcription" or "translation" and then suggest these pathways are somehow altered by natural products without any evidence. This is very misleading for consumers and unethical presentation of bogus data in a scientific publication.
- The authors failed to correctly interpret their own poorly presented figure 2c. For example, the authors mentioned that bacteria found in these products are associated with pathways that are related to energy metabolism, membrane transport etc. which is a very high level of classification without any specifications. The associated heat map shows there are seven pathways with which bacteria are highly (red color) associated and none of those seven pathways are related to diseases. Actually, all the pathways associated with diseases are shown in green which means these detected bacteria are least associated with these pathways.
- It was generated using QIIME and PICRUST
- We have only provided factual results. Our conclusion on the death of our patient due to Herbalife was on clinical DILI based investigational and causality protocol.
- Please do not discuss thyroid hormones again. They do not cause acute liver failure.
- We did not claim microbiota from sourced samples caused death of the patient. Nowhere it is mentioned as such. We have only shown contamination and functional pathways associated with identified species. Please do not assume falsely. Figure 2c is representational of the microbiota identified and we have only mentioned the same. Dr Steven is overly worked up on the Figure that is only supportive but not conclusive. He is missing the 'elephant in the room'.

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### **Additional comments from respected senior scientists:**

- It is unclear from the “Guide to authors” document of this journal if case studies are peer reviewed or not. We noticed mistakes that could be easily identified in peer reviewed process such as 1) number of samples described in legend does not match with what is shown in the figure 2 (HL 2b is missing in figure but mentioned in legend). 2) Bacterial phyla are mentioned in figure 2a but in the legend they were described as families. 3) It was mentioned that Shannon diversity index was used for description of ‘species’ abundance and evenness in a bacterial community. But there was no mention of a single bacterial species in the entire article, at the maximum the relative abundance of genera was presented in the figure. We think publication of far-reaching claims such as “Herbalife-Associated Fatal Acute Liver Failure” should have been subjected to a more rigorous scientific review process. It is unfortunate to see poor science with evident bias from bogus claims published in an Elsevier Journal.
- They did not study or show the evidence of the reported heavy metals, chemical compounds and/or pathogens found in the diseased patient for this reason this article claim has no ground and it should be retracted.
- The heavy metals reported in the paper are having an endpoint effect on kidney rather than liver. The highly claiming research works should have studied all the possible reasons, they should have studied or reported the status of the kidney.
- In our experience with publishing case reports (this is not the first one) with JCEH, case studies are peer reviewed. Such sarcastic statements from Dr Steven are not welcome. Please refrain from personal attacks, and refrain from shaming the journal and publisher as well.
- Repeat question, please see answers in the above section
- Please provide reference to substantiate the statements, Dr Steven. Our patient died of acute liver failure that involve multiple organs in the end stage.
  
- They stated their case study patient had consumed thyroxine supplements for 5 years prior to consuming Herbalife HDS products. However, they did not disclose the drug and conduct any study or at least state the co-relation between thyroxine supplements and HDS products. What if the reaction between thyroxine supplements and HDS caused liver disease and not just HDS alone? There are many research works showing the thyroxine supplement induce liver injury. (<https://livertox.nih.gov/ThyroidHormone.htm>).
- Authors did not report what was the changes and step they made after the initial report of jaundice. Did the patient withdraw the thyroxine supplement/HDS usage? Why the case was worsened? There are many cases reported hypothyroidism related liver injury (Ref 27: Benvenga S, *et al.* 2018, <https://livertox.nih.gov/ThyroidHormone.htm>).
- All the reported elevated levels of enzyme/bile salts in column 1 page 2 shows there is a liver injury but that did show that is due to Herbalife as per their claim in the last line of the same column[Drug-induced liver injury secondary to Herbalife supplement was considered, with Roussel Uclaf Causality Assessment Method score 6 (probable adverse reaction)]. This could be the cumulative/individual effect of the thyroxine supplement/Herbalife HDS. This paper should be retracted for this random claim.
- Very general words “trace/Believe” in line “traces of psychotropic recreational agent” on page 3 column 1 and in page 4 column 2 “We also believe that it is not only the heavy metals but also possible unknown but toxic phytochemical constituents and adulterants that would have aggravated the liver injury in our patient” are just their faith and shows their motivation. Without the exact amount and evidence, the claim lost its value. This report should be retracted.
  
- Please. Read through the LiverTox description on thyroxine and liver injury. It is very different from what has been described in our study. We understand that Dr Steven has to and is trying

very hard to find another cause to blame for the patient's liver injury and death, but to be frank, there is none to blame other than the HDS the patient consumed. The peer review is accurate, was very constructive and above all, scientific in its approach to our case study. And all of Dr Steven false claims and tall paragraphs cannot change it. Did Dr Steven actually read the REF 27 he has quoted? Benvenga et al is on Amyloidosis and hypothyroidism and nothing related to our published study.

- Falsely constructed, twisted statement by Dr Steven. Not valid and the real 'bogus' claim in this whole discussion.
- Lay comments, no requirement for responses.
  
- An error in the table 1. The heavy metal Thallium symbol is Tl, is wrongly written as Th (Thorium).
- The NGS analysis used in this study did not quantify bacterial species/strains, nor differentiate live or dead cells, which is needed to make any claims about whether or not they are pathogenic. The test results do not reflect anything about quality of product. Secondly, the lab and the authors were vague about the specific organisms that might have been detected. Identification of bacteria at the genus level disregards organism specificity and bacterial safety risks. There is no guarantee that they even did testing on Herbalife products. There is no mention of a product batch or reference number. It is surprising that there are no specific methods or data quality metrics to assess if the tests are accurate. Most important we do not know the quality of the DNA sequence reads, which should be provided in a table or at least as a supplemental file.
- NGS method used is not appropriate for this project as it lacks a positive control, is known to have inaccurate estimates of sequence reads (quantification may be biased), and there are considerable PCR bias and bioinformatic issues that are known to cause considerable numbers of false positives for contaminants in processed materials.
  
- Thank you for pointing out the error in Th. As rightly suggested, it is Tl for Thallium. We would make an erratum for the same.
- NGS analysis was robust and as per described literature. Herbalife products were tested as described in the Table and in the manuscript. We are clinicians providing care and comfort for our patients. We do not need to make up stories. All stories, some reported, some not, are real and lived by us, shared through a bond – both with the patient and the family. Accusing authors of a peer reviewed publication with false facts and character assassination is akin to criminal offense that may attract penalty from the authors and the journal.
- It is appropriate. Dr Steven does not provide any strong evidence that makes it otherwise.
- Dr Steven, in his description since the beginning of this letter, did not even bother to address the patient who died or her family who survived through this tragic ordeal. All discussions were on saving and protecting stakeholders. This kind of discussion from a basic scientist itself shows the poor nature of criticism that has been forced upon the authors of the published manuscript and the journal.

## **Review References**

by Dr Steven Newmaster and colleagues

**VERY POORLY REFERENCED**