

TITLE PAGE INFORMATION

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

TITLE:

Title *versus* content. A necessary critical review of the article “Slimming to the death: Herbalife associated fatal acute liver failure ...”

AUTHOR NAMES AND AFFILIATION:

Flávio A. D. Zambrone

Planitox – The Science-based Toxicology Company
Av. José de Souza Campos, 1073
Helbor Offices Sl.801, Campinas, S.P. – CEP.13025-320 – Brasil
flavio@planitox.com.br

Cristiana L. Corrêa*

Planitox – The Science-based Toxicology Company
Av. José de Souza Campos, 1073
Helbor Offices Sl.801, Campinas, S.P. – CEP.13025-320 – Brasil
55 19 2103 6917
55 19 99771 4143
cris@planitox.com.br

Lígia M. S. Amaral

Planitox – The Science-based Toxicology Company
Av. José de Souza Campos, 1073
Helbor Offices Sl.801, Campinas, S.P. – CEP.13025-320 – Brasil
ligia@planitox.com.br

***Corresponding author**

AUTHOR CONTRIBUTIONS

Study conception and design: Zambrone, F.; Corrêa, C.L.
Acquisition of data: Corrêa, C.L.; Amaral, L.M.S.
Analysis and interpretation of data: Zambrone, F.; Corrêa, C.L.
Drafting of manuscript: Corrêa, C.L.; Amaral, L.M.S.
Critical revision: Zambrone, F.

ACKNOWLEDGEMENTS

Dr. Zambrone reports grants from Herbalife Nutrition Brazil, outside the submitted work. The authors work at Planitox that is a Consulting Company in Toxicology and had already provided advisory services in human health area for Herbalife Brazil.

Title versus content. A necessary critical review of the article “Slimming to the death: Herbalife associated fatal acute liver failure ...”

Keywords: hepatotoxicity; causality assessment; RUCAM; Herbalife products

To the Editor,

Philips et al. (2019)¹ report a case of fatal acute liver failure, associated with Herbalife® products. It caught our attention mainly because of the sensationalistic and media-appealing title, in a journal that should necessarily be strictly scientific. The content of the research is shallow, failing to meet minimal scientific quality criteria. The authors cited the work from our research group², however, with partiality, referring only to the numbers of our literature review. They did not consider the aim and central discussion of our work, which consisted in the causality analysis of this type of report, raising awareness on the need for attention and meticulous analysis of the information, thus avoiding mistakes and unsupported conclusions.

Their work does not present details on the history of use of the products under discussion. There are no references on the concomitant use of drugs, alcohol or tobacco, which are common liver risk factors. They reported that the victim used three Herbalife® products that were being consumed at the amounts recommended by the manufacturer. However, for *Afresh Energy Drink*, the serving size mentioned in the paper (10g, twice daily) is not consistent with label recommendations. According to this information, the patient would have been consuming 20X the recommended amount per day, because the recommended serving size is 1g, once per day.

They provided a brief and simplistic description of the chemical, toxicological and microbiological analyses, performed in only 8 samples (n= 1, *Formula 1 Shake*; n=4, *Afresh Energy Drink*; and n= 3, *Personalized Protein Powder*). Data interpretation was hindered, raising doubts on the significance of these samples, the quality of the tests and the adequacy of these findings. The alleged presence of traces of psychotropic substances in 75% of samples was also neither described nor justified. These relevant statements have important implications and should necessarily be discussed in detail, especially because these products must be manufactured under GMP and specific regulations. The identification of the analyzed products' batches is critical in order to make comparisons with the data from the manufacturing laboratory. Such finding, if true, deserves further clarifications and investigation.

The simplistic causality analysis performed did not detail all essential factors for a correct event classification^{3,4}.

The authors also failed to present, with transparency, how they reached the RUCAM score of 6 (probable). Hepatotoxicity was associated with the Herbalife® products used by the patient without even a detailed evaluation on their composition. Only one of them (*Afresh Drink*) seems to contain botanical components (e.g. orange pekoe extract), which required further investigation of a putative association with hepatotoxicity.

Ultimately, the authors did not clarify the objective(s) of their work. In the title, they mix up the report of a clinical case of hepatotoxicity and the possible presence of contaminants in products sold in India. In reality, this refers to a random gathering of information superficially described, not fulfilling any academic or scientific purposes. The paper lacks the critical thinking and impartiality required by science.

REFERENCES

1. PHILIPS C, AUGUSTINE P, RAJESH S, JOHN S, VALIATHAN G, MATHEW J et al. Slimming to the death: Herbalife associated fatal acute liver failure – heavy metals, toxic compounds, bacterial contamination and psychotropic agents in products sold in India. *Journal of Clinical and Experimental Hepatology* 2019; 9(2):268-272.
2. ZAMBRONE F, CORRÊA C, AMARAL L. A critical analysis of the hepatotoxicity cases described in the literature related to Herbalife products. *Brazilian Journal of Pharmaceutical Sciences* 2015; 51(4): 785-796.
3. DANAN G, TESCHKE R. RUCAM in drug and herb induced liver injury: the update. *International Journal of Molecular Sciences* 2016; 17(1): pii E14.
4. DANAN G, TESCHKE R. Drug-Induced Liver Injury: Why is the Roussel Uclaf Causality Assessment Method (RUCAM) Still Used 25 Years After Its Launch? *Drug Saf* 2018; 41(8): 735-743.

ACKNOWLEDGEMENTS

Dr. Zambrone reports grants from Herbalife Nutrition Brazil, outside the submitted work. The authors work at Planitox that is a Consulting Company in Toxicology and had already provided advisory services in human health area for Herbalife Brazil.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

The title defines the content: Reply to critical review by Zambrone et al on Herbalife™ related acute liver failure from India

Cyriac Abby Philips^{1*}, Philip Augustine^{2^}, Sasidharan Rajesh^{3#}

*The Liver Unit and Monarch Liver Lab, Cochin Gastroenterology Group, Ernakulam Medical Center, Kochi, Kerala, India. abbyphilips@gmail.com

^Gastroenterology and GI Endoscopy, Cochin Gastroenterology Group, Ernakulam Medical Center, Kochi, Kerala, India drphilipaugustine@yahoo.co.in

#Interventional Radiology, Cochin Gastroenterology Group, Ernakulam Medical Center, Kochi, Kerala, India rajesh387@gmail.com

Corresponding author

Cyriac Abby Philips MD DM (Hepatology)

Philip Augustine Associates (P) Ltd

Automobile Road, Palarivattom

Kochi, 682025, Kerala, India

Email: abbyphilips@gmail.com

Author contributions: Study concept, design and data acquisition by CAP, PA; drafting of the manuscript by CAP and SR and critical revision by CAP, PA, SR

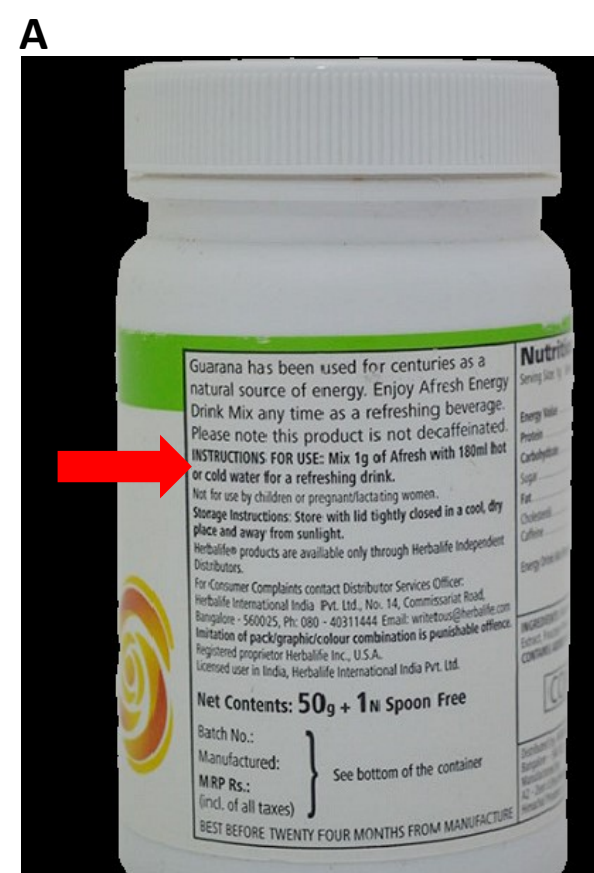
Sir,

We thank Zambrone and colleagues for their interest in our recently published case report on Herbalife Nutrition® (HLN) related acute liver failure in the Journal.(1) We were eager to go through their letter based on the title which stated a 'necessary critical review' of our published study, but were despondent to realize the scantiness of constructive criticism and presence of unsubstantiated 'looming doubts' from the authors which we will gladly address. Zambrone et al concern over the title of the study are unscientific, since they neglect the true content the title projects. The title is truly scientific with regards to representation of factual contents of the study which furthermore, is supported by additional state of the art analysis of similar HLN products. Zambrone and colleagues stated that our study failed to meet minimal scientific quality criteria, when in fact, the study was designed as per CARE Case Reporting Guidelines which they might be unaware. (2) The main reason for our partial description of the critical review by Zambrone et al study on all reported hepato-toxicity cases associated with HLN products in the literature, cited in our published study, was because they were conclusions based on conjecture rather than knowledge and did not merit further deliberation in our discussion. In our published study, we have presented complete details of HLN product use, discussed regarding concomitant drug use and very meticulously excluded all other causes for acute liver failure, including a liver biopsy that did not suggest evidence for alcoholic liver disease, contrary to what Zambrone and colleagues have mentioned in their letter. We invite the authors to go through our published report with more attentiveness and be percipient to finer detail since the title of their letter does not justify its content. The authors wrongly state that the patient consumed HLN products as per manufacturer recommendation. Dose and frequency of consumption were followed as per a 'nutrition club coach' (who are essentially untrained non-medical associates/sellers of HLN) guidance. Zambrone et al also wrongly mention the recommended dose of *Afresh Energy Drink*. The label recommendation for the drink is '1g in 180 ml hot or cold water' [**Supplementary Figure 1A**]. It does not mention the frequency or safe limits for consumption as mentioned by Zambrone et al. The author's discussion in this regard is purely fictional. Furthermore, different HLN associates/sellers recommend doses that conflict with the manufacturer recommendation, as per their discretion –an important aspect our study report sheds light on – unscientific practices mixed with a commercial interest as a public health concern [**Supplementary Figure 1B**]. Our analysis of the HLN products was based on high quality, cutting edge and state-of-the-art methodology which we have already discussed in the published report which leaves no room for doubt regarding our conclusions based on the same. The discussion on butyrolactones which were identified in the HLN products analyzed has been presented in detail which Zambrone et al might have overlooked and we invite them to go through the published report again for clarity

carefully. Our analysis also sheds light on the importance of probable lack of 'Good Manufacturing Practices' and its homogenous maintenance, associated with the HLN product portfolio in various regions and truly deserves further clarification and investigation which we agree to. The causality analysis performed by us (i.e., RUCAM) is the most valid and transparent tool currently in the literature to identify drug-induced liver injury (DILI), and has been endorsed by all National and International hepatology societies including the United States DILI Network. Our reporting has been by the 'minimal requirements for DILI reporting' as per standardized guidelines. (3) The references cited by the authors supporting their statements in this regard are only review-articles that are unpowered. The analysis of HLN products in our report included striking details on mostly undisclosed organic, inorganic and bacterial components with hepatotoxic potential, discussed with clarity. Zambrone et al have repeatedly provided wrong and misleading information regarding HLN products in their letter. They mention that only *Afresh Energy Drink* contains botanical components (orange pekoe extract). In fact, among products consumed by our patient, *Afresh Energy Drink* contains additional green tea extract (a known hepatotoxic agent) and *Formula 1 Shake* contains undisclosed 'natural herbs' as per the official HLN India website product description [Supplementary Figure 1C]. Objectives form part of case series or large observational or randomized studies and not single case reports. The title of our study speaks volumes about its content, is factual and rightfully designed, and closely link our case report to a robust analysis performed on similar HLN products. In reality, the letter by Zambrone et al is far from critical and more of a feeble 'knee-jerk reaction' without scientific acumen, to already known, satisfyingly substantiated and reliable reporting on HLN associated liver toxicity. Ultimately, the true essence of our report was to bring to attention, the unmet need for herbal and dietary supplements to undergo strict testing in clinical trials as for prescription drugs, in the future, in a better world, to improve on public and user health.

References

1. Philips CA, Augustine P, Rajesh S et al. Slimming to the death: Herbalife®-associated fatal acute liver failure-heavy metals, toxic compounds, bacterial contaminants and psychotropic agents in products sold in India. *J Clin Exp Hepatol*. 2019; 9:268-272.
2. Gagnier JJ, Kienle G, Altman DG, et al. The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development. *Glob Adv Health Med*. 2013; 2:38–43.
3. Agarwal VK, McHutchison JG, Hoofnagle JH; Drug-Induced Liver Injury Network. Important elements for the diagnosis of drug-induced liver injury. *Clin Gastroenterol Hepatol*. 2010; 8:463–470.



B

★Morning★ <https://herbalforhealth.co.in/blog/?p=164>

1. Drink Fresh Water
 - 2 – 3 glass of plain water early morning would clean your whole digestive system.
2. Drink Afresh Energy Drink (300 mL)
 - 2 Spoon of Afresh Energy Drink powder in 300 mL of water.
 - You may drink it warm or cold, but it is always recommendable to take it with warm water
3. 15 Mins after Your Drinking Afresh: Take Cell-U-Loss Tablet (100 mL)
 - 1 Cell-U-Loss Tablet 15min after taking Afresh Energy Drink with 100ml normal water.
3. 30 Mins after Your Drinking Afresh: Drink Formula 1 Shake and Personalized Protein Powder (400 mL)
 - 3 Flat spoons of F1(Nutritional Shake Mix) and 2 Flat spoons of F3 (Personalized Protein Powder) in 400 mL normal water or (200 ml toned milk + 200 ml normal water) or (200 ml any fruit juice + 200 ml normal water) .
 - If you decided to use a blender(mixer) to mix them, do not blend for more than 5 seconds or you will damage the nutrients contained in F1.
4. (Optional): ONE Hour after Your Shake: Drink Afresh Energy Drink to achieve more faster weight loss result (300 mL)
 - 2 Spoon of Afresh Energy Drink powder in 300 mL of water.
 - You may drink it warm or cold, but it is always recommendable to take it with warm water

★Afternoon★

1. 15 min before Lunch: Take Cell-U-Loss Tablet (200 mL)
 - 1 Cell-U-Loss Tablet 15min before taking lunch with 200ml normal water.
2. Take Colorfull Lunch
 - Less calories
 - Less oily
 - More colouring vegetables
 - Fruits

** can switch with a Shake if your dinner is a Normal meal.
3. (Optional): ONE Hour after Lunch: Drink Afresh Energy Drink to achieve more faster weight loss result (300 mL)
 - 2 Spoon of Afresh Energy Drink powder in 300 mL of water.
 - You may drink it warm or cold, but it is always recommendable to take it with warm water.
4. UNABLE to Finish the Required Amount of Water per Day by 8 PM?
 - You should not try to reach your water intake goal after 8 PM, just forget it and try again tomorrow.
 - Drinking **NO** water or **just a little bit of water** after 8 PM is to avoid water retention in your body, which will result in gaining water weight.

★Night★

1. Drink Afresh Energy Drink (300 mL)
 - 2 Spoon of Afresh Energy Drink powder in 300 mL of water.
 - You may drink it warm or cold, but it is always recommendable to take it with warm water
3. 15 Minutes after Your Drinking Afresh: Take Cell-U-Loss Tablet (100 mL)
 - 1 Cell-U-Loss Tablet 15min after taking Afresh Energy Drink with 100ml normal water.
2. Drink Formula 1 Shake (400 mL) – No Protein
 - 3 Flat spoons of F1(Nutritional Shake Mix) in 400 mL normal water or (200 ml toned milk + 200 ml normal water) or (200 ml jouce of any frouit + 200 ml normal water) .
 - If you decided to use a blender(mixer) to mix them, do not blend for more than 5 seconds or you will damage the nutrients contained in F1.

C

Formula 1 Nutritional Shake Mix

Description:

Formula 1 Nutritional Shake mix makes a great tasting shake, specifically formulated with all necessary quality soy protein isolate, as Nutritional Food product for nutritional requirements. Packed with vitamins & minerals along with natural herbs, antioxidants and dietary fiber, it provides desired protein and nutrition without overloading unnecessary fat and calories. One serving of Formula 1 shake mix provides 90 kcal of energy. Enjoy Formula 1 shakes once or twice a day along with portion controlled nutrition and exercise to help towards keeping the body fit.

Formula 1 Nutritional shake mixes are tested for Glycemic index (GI) and test result confirms it as low GI*

**F1 Nutritional shake mixes are tested for low GI by Temasek Polytechnic, Singapore

SKU # 1247 Flavor French Vanilla

Previous [View All](#) Next

Afresh Energy Drink Mix

Description:

Afresh energy drink mix contains Orange Pekoe extract, green tea extract and natural caffeine powder. Caffeine helps you feel energized, supports alertness. Enjoy as a refreshing beverage at any time of the day

SKU # 1291 Flavor Ginger
SKU # 1294 Flavor Elaichi
SKU # 1295 Flavor Lemon
SKU # 1296 Flavor Peach
SKU # 1238 Flavor Cinnamon

FSSAI Lic No. 10013043000639
MRP: Rs. 666.00 (inclusive of all taxes)

[Order from an associate](#)

Supplementary Figure Legend:

Figure 1 – A: Label recommendation for *Afresh Drink* consumption; **B:** subjective and unrecommended prescription for product use; **C:** undisclosed and undefined additional herbal ingredient mentioned in product description on Herbalife® Indian website.