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Reports alleged to be associated with an Herbalife food product are not properly evaluated for alternative etiologies.

In a thesis published by Mengual Moreno in February 2014, the author assesses 13 cases of liver injury reportedly observed in a hospital in Zulia, Venezuela (1). The author implicates various products amongst these case reports including Herbalife's Formula 1 meal replacement shake (registered as a food in Venezuela).

The information provided in the manuscript does not substantiate a causal relationship between the consumption of Herbalife's Formula 1 shake and either of the two different presentations (one cholestatic and one hepatocellular liver injury) which are being attributed to DILI. However, both of the patients who reportedly consumed Formula 1 presented with significant health histories including a 52-year old female who was morbidly obese and a 36-year old male with Human Immunodeficiency Virus (HIV). Clearly both conditions may be associated with a myriad of medical complications. In the case of a morbidly obese individual, concomitant medication use, fatty liver disease, heart failure, and/or concurrent pancreatic disease are amongst the likely underlying etiologies which could have caused or contributed to the reported presentation and fatality although none of these potential factors appear to have been ruled out in the report. In HIV patients, liver-related complications are actually quite commonly associated with the anti-retroviral therapies used to treat the condition and/or other liver diseases which can stem from any number of opportunistic infections which these patients are especially susceptible to (depending on the stage of the disease, health management, etc). These etiologies were also not properly ruled out and none of the clinical presentations were described to ascertain whether the signs and symptoms were in fact consistent with DILI as opposed to other potential factors. Additionally, Hepatitis E was not considered in the viral serology screening and not only is this condition a growing concern worldwide, but it can also present very similarly to DILI. Furthermore, the omission of definitive testing such as a liver biopsy is negligent especially given the pre-existing history and numerous risk factors in each of the two Herbalife consumers.

It is also important to acknowledge Herbalife has published several rebuttals in the Journals, including those referenced in this thesis, which have alleged an association between the consumption of our products and liver disease over the last several years (2-11). In fact, some third party experts which are unaffiliated with Herbalife have been questioning the validity of the negative articles and conclusions associated with Herbalife's brand (12, 13). To that end, the mere existence of the allegation does not objectively or scientifically establish causation and it is important to recognize that no specific Herbalife product or ingredient has been identified as causally associated with the cases published to date in addition to the fact that there have been no proposed mechanisms to suggest physiological plausibility. Formula 1 was even the subject of a study by Feder et al (7) with an intention to prove hepatotoxicity and they failed to show any hepatic impairment in the subjects (rats) consuming this product during the study. Herbalife published a rebuttal to the authors' biased and subjective conclusion that negated the clear findings established by this study (i.e. Formula 1 was not found to be hepatotoxic when consumed in a randomized controlled study environment). In addition, a Formula 1 study conducted at University of

California, Los Angeles showed no adverse effects on the liver, kidney, or bone density when consumed by the participants (human) (14).

The Roussel Uclaf Causality Assessment Method (RUCAM)(15)used by the authors is also inaccurate given the fact that Formula 1 has no established history of liver-related incidence and relevant etiologies were not ruled out (both considerations would significantly impact RUCAM scoring). However, the RUCAM scoring cannot be recalculated in the absence of additional information, including the transaminase recovery patterns of each consumer.

Finally, it should be noted that the thesis presents only 13 cases which presented over approximately a one-year duration of which only 2 of the 13 patients happened to be Herbalife consumers who reported consuming Formula 1. In fact, the author acknowledges, 'the results of this study are not representative of the population of the state of Zulia'(1). This is not surprising given the enormous amount of Formula 1 consumption in the country – more than 2.6 million units of Formula 1 were sold in Venezuela in 2013 alone. Considering the aforementioned risk factors which existed in each of the two Herbalife consumers, the insufficient clinical information provided for each of these two patients, and the arbitrary assumptions of the author that "Herbalife" is associated with liver injury based on dated and debated Journal articles, the thesis presents a very poor argument for a causal association with Formula 1.

In conclusion, we would suggest that only a temporal/coincidental association may be established between the reported events and the consumption of Formula 1 based on the information published by the thesis author to date.

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