Chemical Considerations Regarding the H-Value Methodology and Its Relation With Toxicity Determination

We are writing about the recently published paper “How to ward off retinal toxicity of perfluorooctane and other perfluorocarbon liquids?” by Menz et al. The article is of great interest to us and other vitreoretinal surgeons because of the huge number of cases in which blindness has occurred after vitreoretinal surgery during which perfluorocarbon endotamponades were used. The perfluorocarbon (PFO) liquids were manufactured by different companies, one German, one Indian, and one Turkish. The existence of these toxic compounds and the insufficient control by European Union authorities were also part of a report made by the International Consortium of Journalists that was released in many mass media outlets in Europe in December 2018, causing alarm among patients and ophthalmologists.

In their article, Menz et al. reported an analytical method to determine the concentration of incompletely fluorinated compounds assuming that its presence is the cause of cytotoxicity, increasing in a dose-dependent manner. We found several aspects that need clarification in the referenced paper. The basis of any scientific publication is that the analytical procedures should be easily reproduced in any laboratory in the world. Thus, an essential feature of any published report is the absolute clarity and accuracy of the methodology. In this sense, we have some issues about the methods, as detailed below.

When a digestion process to cleavage C-F bonds from a complex molecule is performed, it is important to calculate the yield of the reaction to ensure that all of the fluoride ions are extracted during the digestion. In the reported experiments, the yield was not calculated, nor was it reported in the literature cited in the references. The reaction was not evaluated to ensure that the three fluoride ions were always released. Further, it is doubtful that the amine used in the protocol could easily break the C-F bonds. This is an important issue because the stoichiometric factor 1/3 is used in the equation to calculate the concentration of incompletely fluorinated contaminants.

Moreover, as the methodology is described, it seems to be specific to those compounds with only one or two C-H bonds in the perfluorocarbon molecule. Other contaminants, such as the -COOH (acid group), with high toxicity have been found in the perfluorocarbon molecule. Other contaminants, such as the -OH, perfluorooctanoic acid, and/or dodecafluoro-1-heptanol, which have been identified in this study. The existence of these toxic compounds and the insufficient control by European Union authorities were also part of a report made by the International Consortium of Journalists that was released in many mass media outlets in Europe in December 2018, causing alarm among patients and ophthalmologists.

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**Figure.** Graphic interpretation of the procedure followed by Menz et al. to establish the dose dependency between H value and cytotoxicity. Different amounts of “pure” PFO with a H-index of 10 ppm were added to the original AlaOcta toxic sample lot 061014. By doing that, H-index was reduced, but also the concentration of the contaminants not related to incompletely fluorinated compounds present in the above-mentioned lot.