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March 1, 2012

Mr. Dirceu Brás Aparecido Barbano
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Dear Mr. Barbano:

I understand that ANVISA has under consideration a proposal that would prohibit the use of a list of specified additives in cigarettes. I understand that in connection with ANVISA's consideration of this proposal representatives of one or more tobacco companies have circulated a paper entitled "Scientific assessment of the use of sugars as cigarette tobacco ingredients: A review of published and other publicly available studies" by Ewald Roemer and colleagues (*Critical Reviews in Toxicology* doi:10.3109/10408444.2011.650789) from Philip Morris International. The overall conclusion of this paper is "examination of the data available suggests that the use of sugars as ingredients in cigarette tobacco does not increase the inherent risk and harm of cigarette smoking."

I have reviewed the paper and find that the conclusion stated above is both inaccurate and misleading. Indeed, a careful reading of the information in Philip Morris' paper shows that the information presented does not support Philip Morris' conclusion that the use of sugars as additives in cigarettes does not increase the inherent risk and harm of cigarette smoking.

- Although the Philip Morris asserts that "there is no practical possibility of the small amounts of unchanged sugars in smoke to contribute to the initiating and addicting potency of smoking," this conclusion is directly contradicted by the statement in the next paragraph that "the use of sugars positively adds to the overall sensory perception of tobacco smoke."
- Philip Morris downplays the interaction between acetaldehyde (which three studies cited in the paper show increase when sugar is added; see their Table 3) and nicotine which interacts with nicotine to increase the addictive impact of the tobacco product.
- The paper notes, but downplays, increases in several important toxins associated with the addition of sugar: formaldehyde, acrolein, 2-butanone, isoprene, benzene, toluene and

benzol[a]flouranethene. Increases in these substances should concern both regulators and the public given their adverse effects on human health.

- The presentation of results is done in such a way that obscures evidence that additives—and particularly sugar—increases both the toxicity of the smoke and the “overall [positive] sensory perception of tobacco smoke,” which makes cigarettes more palatable and attractive.

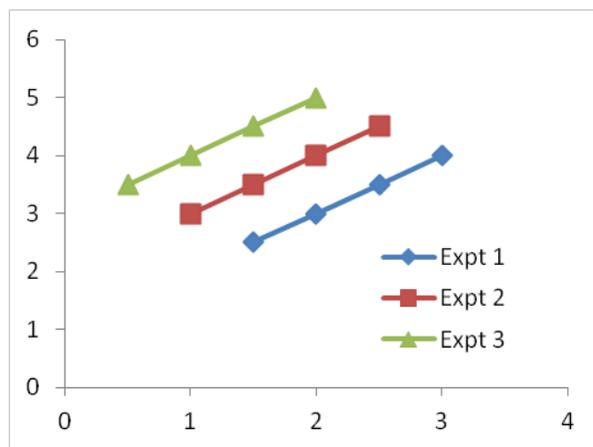
Regulators should not rely on this paper to provide a scientific basis to conclude that added sugars do not increase the risk or addictiveness of tobacco products. Indeed, the information in the Philip Morris paper actually supports the opposite conclusion.

Not surprisingly, this paper uses essentially the same methodology and suffers from the same biases that we found in our analysis of Philip Morris’ Project Mix analysis of groups of cigarette additives (Wertz et al, The toxic effects of cigarette additives. Philip Morris' project Mix reconsidered: an analysis of documents released through litigation. *PLoS Med.* 2011 Dec 8 (12): e1001145; copy attached). In that paper we found the conclusions that additives did not affect the toxicity of cigarette smoke were **not supported** by the evidence that Philip Morris collected. The new sugar paper suffers from the same problems as Project Mix that make the conclusions that the additives did not increase cigarette toxicity unreliable:

- The assays used for cytotoxicity were used to assess dose-response, even though these assays are for screening not assessment of dose-response.
- The toxicology studies are based on small numbers of rats (generally 10 per group), which means that the studies have low ability (what statisticians call “power”) to detect toxic effects should they exist. (The number of rats was not reported in the Philip Morris sugar paper; I had to look in the papers they were citing.) This fact means that one cannot have confidence in the negative conclusions that the authors drew.
- While the smoke chemistry studies in the sugar paper were analyzed on a per nicotine basis (as opposed to a TPM basis in Project MIX), like Project MIX the toxicology studies were done on a per total particulate matter (TPM) basis, which understates the toxic effects.

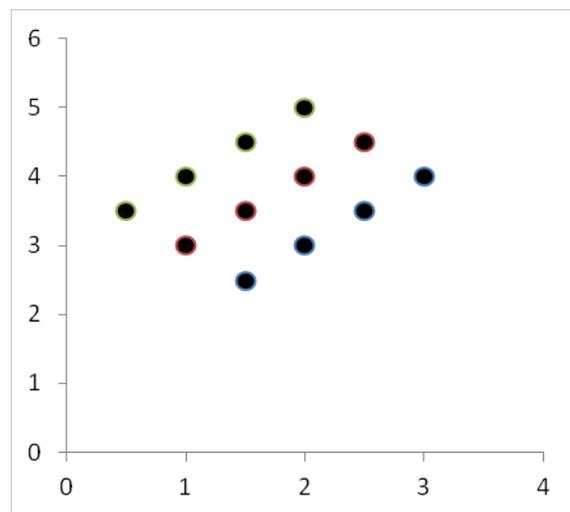
The way that Philip Morris pooled the results from several studies on the effects of adding sugar on the presence of toxic chemicals in the smoke produced from cigarettes with the sugar added (Table 3 and Figure 3) obscures the actual effects of adding sugar. The problem is that the Philip Morris analysis does not account for the fact that there were differences between different studies (as evident from looking at Figure 3 in their paper) and their analysis did not account for these differences.

To understand why, suppose that we did three different experiments on the relationship between added sugar and some chemical, say Toxin A where more added sugar leads to more Toxin A in each experiment, but from different starting points as shown in the graph to the right. Allowing for differences between the different



experiments clearly shows this consistent relationship.

Rather than allowing for those differences in the pooled analysis (something for which there are standard statistical methods available in common statistical computer packages), Philip Morris ignored these between-experiment differences and just did a single straight line fit to the data, so the differences between the experiments obscured the consistent effects within each experiment as shown in the graph to the right. This problem with the way that Philip Morris did their statistics probably explains why, for example, they reached an overall negative conclusion for the effect of added sugars on the amount of acetaldehyde and propionaldehyde even though several of the individual studies showed increases.



This failure to account for differences between individual studies also likely explains why Philip Morris reported an overall negative effect of adding sugars on N-nitrosodimethylamine despite the fact that one of the individual studies showed an increased effect and the other showed no effect. This odd result should have indicated to Philip Morris' scientists that there was a problem with their analysis.

The fact that Philip Morris did not account for these differences is particularly surprising since virtually any statistical package will handle such an analysis.

Despite the problems with the way that the data were analyzed, Philip Morris did find increases in several important toxins associated with the use of sugars: formaldehyde, acrolein, 2-butanone, isoprene, benzene, toluene, and benzol[a]flouranethene.

As noted in the summary above, the paper stated (on page 7, second column) that “there is no practical possibility of the small amounts of unchanged sugars in smoke to contribute to the initiating and addicting potency of smoking.” This statement seems to be directly contradicted in the next paragraph, which states, “the use of sugars positively adds to the overall sensory perception of tobacco smoke.”

Philip Morris also ignores the interaction between acetaldehyde (which three studies show increases with added sugars in Table 3) and nicotine to affect nicotine metabolism. This is a very important effect in terms of the relationship between added sugars and the addictive potential of cigarettes.

It is also important not to take the way that Philip Morris characterizes the work of other scientists. For example, consider how Philip Morris represents interaction of acetaldehyde and nicotine on page 13 of their paper:

This conclusion [that adding sugars to cigarettes does not increase acetaldehyde] is important considering the *suggestions* that sugars could be added with the intention to increase the yield of acetaldehyde so as to increase the addictive potency of cigarette smoke by interacting with nicotine or by the formation of derivatives with biogenic

amines (Belluzzi et al., 2005; Talhout et al., 2006; Rabinoff et al., 2007; Talhout et al., 2007; European Commission Health and Consumer Protection Directorate-General Scientific Committee on Emerging and Newly Identified Health Risks, 2010). [emphasis added]

This is a misrepresentation as the papers Philip Morris quotes actually go far beyond “suggesting” that acetaldehyde affects nicotine [emphasis added]:

- Belluzzi, et al 2005: ... acetaldehyde, at the low concentrations found in tobacco smoke, **interacts with nicotine to increase responding in a stringent self-administration acquisition test where nicotine alone is only weakly reinforcing**, and that adolescent animals are more sensitive to these actions than adults. Animal models of tobacco addiction could be improved by combining acetaldehyde ... with nicotine to more accurately reflect the pharmacological profile of tobacco smoke.
- Talhout et al, 2006: In particular, **sugars increase** the levels of formaldehyde, acetaldehyde, acetone, acrolein, and 2-furfural in tobacco smoke. It is concluded that **sugars in tobacco significantly contribute to the adverse health effects of tobacco smoking**.
- Rabinoff, et al, 2007: Our findings indicated that more than 100 of 599 documented cigarette additives have pharmacological actions that camouflage the odor of environmental tobacco smoke emitted from cigarettes, enhance or maintain nicotine delivery, **could increase the addictiveness of cigarettes**, and mask symptoms and illnesses associated with smoking behaviors.
- Talhout, et al, 2007: Thus, **acetaldehyde may increase the addictive potential of tobacco products** via the formation of acetaldehyde-biogenic amine adducts in cigarette smoke and/or in vivo, but further research is necessary to substantiate this hypothesis.
- European Commission Health and Consumer Protection Directorate-General Scientific Committee on Emerging and Newly Identified Health Risks, 2010: ... sugars added in high quantities to most tobacco products, **give rise to numerous aldehydes**, such as acetaldehyde, in tobacco smoke. Acetaldehyde given intravenously is self-administered and enhances the addictiveness of nicotine in experimental animals.

Philip Morris uses the analysis of the effects of added sugar on smoke chemistry (Table 3) as the basis for simulations of the effects of added sugars on human exposure to several toxins. Given the problems with the analysis discussed above, the input information into their models is unreliable, so are the conclusions of their modeling exercise.

It is also important to note that the majority of studies that Philip Morris cites in its sugar paper are published by tobacco companies or organizations funded by tobacco companies (see attached annotated bibliography). The tobacco industry has a long, well-established pattern of selective publication and suppression of unfavorable results. Federal Judge Gladys Kessler cited this *ongoing* pattern of behavior in her decision finding that the major US cigarette companies (including Philip Morris) had formed an illegal racketeering enterprise to defraud the public. Manipulation of science was a key element of Judge Kessler’s decision (see attached excerpts). When considering the reliability of Philip Morris’ presentation of scientific evidence it is important that you (and all regulatory authorities everywhere in the world) consider that Philip Morris remains under Judge Kessler’s jurisdiction because both she and the Court of Appeals concluded that past racketeering activities were continuing and likely to continue in the future.

Like Project Mix, Philip Morris’ paper, “Scientific assessment of the use of sugars as cigarette tobacco ingredients: A review of published and other publicly available studies,” is

another example of designing a study and presenting the results in a way that obscures the evidence that this additive is likely increasing the toxicity of the smoke and the “overall [positive] sensory perception of tobacco smoke.” Indeed, a careful reading of Philip Morris’ paper reveals that it (1) confirms that addition of sugar to cigarettes increases the level of many toxins; (2) downplays the evidence that addition of sugars increases the addictive nature of cigarettes; and (3) concedes that addition of sugars makes cigarettes more attractive to consumers by enhancing the overall sensory experience.

The information in this paper did not change the fundamental conclusion of our paper on Project Mix: “regulatory authorities, ... who are implementing FCTC articles 9–11, could use the Project MIX data [and, for that matter, the data in the sugar paper] to eliminate the use of ... additives ... in cigarettes. Any tobacco company would, of course, remain free to submit an application to [any] regulatory agency, to reintroduce use of an additive if they could provide convincing data from adequately powered studies that the additive truly did not have any adverse health consequences.”

I hope this information is helpful and would be happy to answer other questions you have.

Best wishes,



Stanton A. Glantz, PhD
Professor and Director

cc: Maria Cecilia Martins Brito
Jose Agenor Alvares da Silva
Jaime César de Moura Oliveira