

**PMI's MRTP application for IQOS does not adequately evaluate potential for hepatotoxicity risk**

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Philip Morris International (PMI) has recently submitted an application to market the IQOS as a “modified risk tobacco product” (MRTP). The IQOS, PMI’s addition to a growing class of “heat-not-burn” (HNB) tobacco products, is designed to allow users to maintain the sensory feel of smoking while decreasing exposure to the harmful toxicants found in conventional cigarette smoke. The *in vivo* toxicology data from Module 7 of PMI’s MRTP application includes extensive studies focusing on pulmonary and cardiovascular endpoints. In this regard, PMI has presented evidence that it represents as showing decreased pulmonary and cardiovascular toxicity of the IQOS, relative to conventional cigarettes. PMI’s representations ignore the fact that in clinical studies of American people for 23 of 24 biomarkers of potential harm, including several related to pulmonary and cardiovascular toxicity are not significantly different between IQOS and conventional cigarettes.<sup>1</sup> In addition, having reviewed the *in vivo*

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<sup>1</sup> PMI’s Own Data on Biomarkers of Potential Harm in Americans Show that IQOS is Not Detectably Different from Conventional Cigarettes, so FDA Must Deny PMI’s Modified Risk Claims. Public comment submitted by SA Glantz to FDA on PMI’s Modified Risk Tobacco Product application for IQOS. Tracking number 1k1-8zrx-juh9. Available at <https://tobacco.ucsf.edu/pmi%E2%80%99s-own-data-biomarkers-potential-harm-americans-show-iqos-not-detectably-different-conventional-cigs>

toxicological profile in detail, we are concerned *that IQOS may have unanticipated qualities of toxicity that merit further studies of long-term product safety.*

*By focusing solely on endpoints informed by the established toxicity of cigarettes, PMI has failed to consider the potentially unique toxicities of IQOS.* In particular, we are concerned by multiple instances of data indicating that *exposure to IQOS emissions might have hepatotoxic effects.* Based on toxicology data from Module 7 of the application, rats exposed for several months to IQOS show significant increases in liver transaminases (AST and ALT).<sup>2</sup> Furthermore, liver weights are increased<sup>3</sup> and hepatocellular vacuolization<sup>4</sup> is observed, suggesting the possibility of metabolic enzyme induction. *Notably, hepatotoxicity was not observed even with the highest levels of CC smoke exposure tested,<sup>5</sup> which suggests that, on this dimension, IQOS may be more dangerous than conventional cigarettes.*

*The clinical data provides further cause for concern.* In PMI's clinical studies of 22 healthy volunteers, 5% of subjects had increased levels of bilirubin.<sup>6</sup> Given the findings of hepatotoxicity in rats, it is possible these conditions are in fact related to IQOS exposure. *For the sake of consumer safety, it is critical that this unanticipated hepatotoxicity be explored in greater detail prior to allowing PMI to market this technology as a reduced or modified risk tobacco product.*

*It is possible that IQOS exposure would further increase risks of hepatotoxicity for users ingesting common medications like acetaminophen (and other cytochrome P450 altering*

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<sup>2</sup> Module 7.2, Preclinical In Vivo 90dReg Report Manuscript, Table 6

<sup>3</sup> Module 7.2, Preclinical In Vivo 90dReg Report Manuscript, Table 10

<sup>4</sup> Module 7.2, Preclinical In Vivo 90dReg Report Manuscript, Table 14

<sup>5</sup> Module 7.2, Preclinical In Vivo 90dReg Report Manuscript, Table 6

<sup>6</sup> Appendix A6.1.5.4

*drugs), and substances such as alcohol.* Given the high rates of alcohol use among smokers,<sup>7, 8</sup> this is an area of particular concern.

Section 911(g) of the Family Smoking Prevention and Tobacco Control Act provides that FDA may issue a MRTP order *only if* PMI has demonstrated that IQOS, *as actually used by consumers*, will “(A) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and (B) benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.” *Since PMI’s studies failed to adequately evaluate the hepatotoxicity of IQOS, and failed to consider how the product might be “actually used by consumers,” including significant evidence that smokers have high rates of alcohol use, FDA must deny PMI’s MRTP application.*

*Section 911(d) is clear and unambiguous about the evidence an applicant must provide before FDA can issue an MRTP, including all research findings and scientific information “relating to the effect of the product on tobacco-related diseases and health-related conditions, including information both favorable and unfavorable to the ability of the product to reduce risk or exposure and relating to human health.”* However, despite the signals contained within their *in vivo* and clinical data, *discussion of potential hepatotoxicity is notably absent from the many executive summaries and manuscripts that comprise PMI’s MRTP application.*

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<sup>7</sup> Drobes, 2002 Drobes, D. J. (2002). "Cue reactivity in alcohol and tobacco dependence." Alcohol Clin Exp Res **26**(12): 1928-1929.

<sup>8</sup> Batel, 1995 Batel, P., F. Pessione, C. Maitre and B. Rueff (1995). "Relationship between alcohol and tobacco dependencies among alcoholics who smoke." Addiction **90**(7): 977-980.

Until this matter has been thoroughly examined, it would be dangerous to allow PMI to label or market IQOS as a reduced or modified risk product. For this reason, ***we strongly recommend that FDA denies PMI's MRTP application.***