Possible hepatotoxicity of IQOS

On 25 January 2018, the Food and Drug Administration (FDA) Tobacco Scientific Advisory Committee unanimously voted (with one abstention) that Phillip Morris International (PMI) could not claim their heated tobacco product (HTP) IQOS (I-Quit-Ordinary-Smoking) would reduce the risk of tobacco-related diseases. Regardless, IQOS is already available in over 30 countries, and thus merits scrutiny from the scientific and medical communities. The preclinical and clinical data PMI submitted to FDA indicate that IQOS exposure may be associated with unexpected liver toxicity. We reviewed preclinical studies conducted by PMI scientists[1] and clinical studies of 5 and 90 days of exposure to IQOS and IQOS menthol[2–5] included in PMI's Modified Risk Tobacco Product application submitted to the US FDA.

Wong and colleagues[1] exposed 92 male and 92 female Sprague Dawley rats to up to 90 days of mainstream aerosol from IQOS, mainstream smoke from 3R4F research cigarettes, or room air (sham). After 90 days of exposure, liver weights and blood levels of alanine aminotransferase (ALT) were measured. ALT is an enzyme released into the blood by hepatocytes during hepatocellular injury[6] and liver weight is a sensitive measure of hepatocellular hypertrophy.[7] After 90 days, ALT levels and liver weights were significantly higher with IQOS than with conventional cigarettes in female animals (table 1). Hepatocellular vacuolisation, a sign of acute liver injury,[7] was significantly increased in IQOS-exposed female rats, an effect not seen in cigarette-exposed animals (table 1).

The human clinical data PMI submitted to FDA provide further cause for concern. Increased plasma bilirubin may signify cholestatic liver injury with impaired hepatic bile flow, accelerated red blood cell destruction, or decreased bilirubin metabolism.[7] Following 5 days of exposure to IQOS, conventional cigarettes or smoking abstinence, plasma bilirubin was elevated in 8.8% of IQOS subjects compared with 0% of cigarette smokers and 2.6% in abstainers.[2] In another 5-day study, the mean increase in ALT was higher with IQOS than with conventional cigarettes or smoking abstinence (4.5, 2.9 and 1.6 IU/L, respectively).[3] In a 90-day study of exposure to mentholated IQOS, mentholated cigarettes or smoking abstinence, the only subject experiencing a grade 2 (moderate) increase in ALT was in the IQOS group.[4] In another study, the rate of grade 1 (mild) increases in ALT after 60 days of exposure was highest with IQOS at 6.3% compared with 0% for conventional cigarettes and 2.6% with smoking abstinence.[5]

Hepatotoxicity constitutes a broad spectrum of injuries to the liver, with consequences ranging from asymptomatic lab abnormalities to hepatic failure and death.[6 7] Notably, there is some evidence that smoking cessation may be associated with a small increase in the unconjugated fraction of bilirubin over the next 1–4 weeks, averaging 0.06 mg/dL.[8] However, in the 5-day exposure study cited above, the rate of elevated bilirubin (>1.0 mg/dL) in IQOS users was over three times higher than that observed with smoking abstinence (8.8% vs 2.6%), and the mean increase above baseline was 0.05 mg/dL with IQOS compared with −0.07 mg/dL with smoking abstinence.[2] We can find no evidence in the literature that smoking cessation is associated with an increase in ALT.

Taken together, PMI's preclinical and clinical data constitute a concerning pattern of possible hepatotoxicity, especially considering the short period of exposure. These findings indicate IQOS may have unexpected organ toxicity that has not been associated with cigarettes. Although IQOS exposes users to lower levels of many toxins than conventional cigarettes, it exposes users to higher levels of other toxins (St Helen *et al*, submitted manuscript). Given the potential for synergistic hepatotoxicity with other medications (eg, acetaminophen), alcohol[9 10] and herbal supplements, the public health community should focus intense scrutiny on possible liver injury in users of IQOS and other HTPs. A broader implication of this finding is that health assessments of IQOS and other non-cigarette tobacco products should consider possible toxicities not associated with conventional cigarettes.

Table 1 Liver parameters in Sprague Dawley rats after 90 days of exposure

	Female			Male		
	Sham	IQOS	3R4F	Sham	IQOS	3R4F
ALT levels (IU/L)	51.0±4.4	73.0±3.2**,****	54.0±2.6	57.0±6.5	75.0±6.7*	68.0±5.8
Liver weight†	339.6±6.6	442.6±10.2***,****	386.7±15.1*	329.3±5.1	381.7±13.2**	373.0±7.9***
Hepatocellular vacuolisation	0.7±0.4	1.5±0.2*	1.2±0.3	1.4±0.3	0.8±0.4	1.8±0.8

Data are from Wong *et al*[1] and are presented as mean±SEM.
*P<0.05 relative to sham; **P<0.01 relative to sham; ***P<0.001 relative to sham; ****P<0.01 relative to 3R4F.
†Normalised to body weight and reported as $\times 10^{-4}$.
ALT, alanine aminotransferase.

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