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PMIs' mouse study demonstrates increased morbidity and mortality in mice exposed to IQOS aerosol, and PMI's December 20, 2019 response to FDA's Request for Information fails to show otherwise

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On January 24, 2020 FDA posted an amendment to Philip Morris International's (PMI) Modified Risk Tobacco Product (MRTP) applications for its IQOS heated tobacco product. The amendment was a December 20, 2019 summary report prepared by PMI in response to FDA's November 20, 2019 Request for Information about PMI's *in vivo* study on lung cancer tumorigenesis in A/J mice exposed to IQOS aerosol. The study showed an increase in morbidity (PMI uses the term "moribundity") and mortality in the A/J male mice exposed to the IQOS aerosol. PMI's summary report tried to rationalize this result by claiming that the result "was not plausibly related to the [IQOS] aerosol but rather is a strain-specific finding."

PMI argued that "the increased early moribundity/morbidity observed in the male mice exposed to high levels of [IQOS] aerosol was due to a strain-specific susceptibility in the male urogenital tract," i.e., male A/J mice are different from their female counterparts in terms of susceptibility to impairment of the urogenital tract. PMI argued that this is most likely due to the *sister x brother* mating scheme in the inbred colonies their study used, and that the mortality due to congenital abnormalities in the urogenital tract of this inbred mouse strain "has limited relevance" to humans. Further, PMI argued that they could not identify putative factors in IQOS aerosol that might be responsible for this result. However, PMI also concluded that the mechanism for this finding remains "elusive," and that this problem did not occur in their rat studies.

Despite PMI's attempts to obscure the results of its own study, ***the data show that A/J male mice exposed to IQOS aerosol have a serious adverse event.***

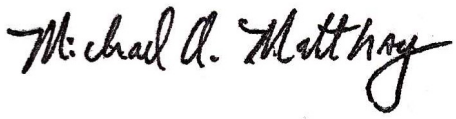
PMI's statement that a causal link to IQOS aerosol cannot be established contradicts their own findings in their studies.

The hypothesized link to a problem with *sister x brother* inbreeding is just a hypothesis. PMI provides no studies that prove or disprove this idea. And even if this inbreeding contributed to the result, it would still be relevant that it occurred in the male mice exposed to IQOS aerosol. (continued)

After more than 40 years of experience conducting research using mice and publishing more than 500 research papers concerning the pathophysiology of acute lung injury and pulmonary edema, I feel qualified to say that since PMI chose the A/J mice for these studies, they have to stand by their results.

FDA properly flagged this problem and asked the right question. PMI's response is not satisfactory. This exchange further demonstrates why FDA should deny PMI's MRTP applications and should not allow PMI to market IQOS with MRTP claims.

Sincerely,



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