Evaluation Summary of Invert Sugar for Use as a Cigarette Ingredient

Invert sugar is an aqueous solution of inverted or partly inverted sucrose. It is accepted as generally recognized as safe (GRAS) by the U.S. Food and Drug Administration for use in food (21 CFR § 184.1859). Invert sugar, with its primary carbohydrate constituents of fructose, glucose, and secondary content of sucrose, provides a pleasing taste (or sweetness) and contributes to the texture and palatability of many foods. It also represents a major source of energy in the typical North American diet. Invert sugar, while once popular as a sweetener in the soft drink industry prior to the introduction of high fructose corn syrup, continues to be used as a sweetening agent in both the baking and confectionery industry.[1]

According to all conventional tests, at present dietary levels, invert sugar is of low toxicity to both animals and humans.[2-10] Studies on the effects of invert sugar on glucose tolerance, diabetes, cardiovascular disease (including hypertension), blood lipids, mineral balances, copper nutriture and suspected cancer incidence in both human and animal studies, point to only transient effects seen with dosages of invert sugar which far exceed the normal dietary intake in humans.[11-64] Factors which weigh heavily on the results of these studies, and are considered confounding factors, are the contribution of abnormal calories with resulting obesity, which itself, is a contributing factor to hypertension, cardiovascular diseases and diabetes. Thus, there are no studies which have been conducted that provide scientific evidence that consumption of invert sugar at concentrations which occur in the average diet directly causes diabetes, hypertension, cardiovascular disease, blood lipid diseases, copper deficiency, reproductive abnormalities or cancer.[65-116]

Currently, invert sugar is used worldwide at levels below 50,000 ppm in selected cigarette brands manufactured and/or distributed by Philip Morris USA Inc. (PM USA) and/or Philip Morris Products SA (PMP SA). Invert sugar is applied directly to the tobacco as a flavor, and as such, invert sugar may be subject to pyrolysis reactions when smoked. Invert sugar may also be applied to the filter as a flavoring material where it would not be subjected to pyrolysis temperatures.

As suggested by the purge and trap studies conducted by PMUSA,[117] invert sugar applied to tobacco would not be expected to distill at 100°C and a significant portion of the material would be available for pyrolysis. At the higher temperautres used in the PM USA pyrolysis studies,[118] the major peaks were identified as furfural, 5-(hydroxymethyl)-2-furfural and levoglucosan. Formaldehyde, acetaldehyde, furan, and carbon dioxide peaks were also identified in the pyrolysis study and these peaks are consistent with pyrolytic destruction of carbohydrate materials. An extensive review of the literature suggests little evidence that supports acetaldehyde as a major pyrolysis product of sugar.[119]

A PM USA study of the chemical analysis of smoke from cigarettes to which invert sugar was added (25,000, 50,000 or 100,000 ppm invert sugar on tobacco) revealed occasional changes (decreases and increases) in some analyzed parameters. Despite the indications of statistically significant changes for some smoke chemistry parameters in test cigarettes compared to the control cigarette, the increase or decrease in yields that were noted probably reflect variability in normal cigarette construction and/or chemical analysis technique. The majority of the

constituents (with the exception of NPY, 4-aminobiphenyl, and formaldehyde) of the constituents fell within the 95% confidence intervals range for the control cigarette. This suggests that normal variation in manufacturing practices could account for the smoke content variability. Due to unknown reasons, levels of NPY and 4-aminobiphenyl were outside of the lower 95% C.L. and the decrease in this two compounds were independent of the invert sugar content in cigarettes. However, formaldehyde at high levels of invert sugar fell outside of the upper 95% C.L., and increases of this aldehyde could be dependent of the invert sugar content[120]. Analysis of the smoke atmosphere generated with these same cigarettes during a 13-week smoke inhalation study indicated that the mean acetaldehyde, acrolein, and propionaldehyde concentrations were comparable between control and test cigarette groups; however, mean formaldehyde concentrations increased with increasing levels of invert sugar. [123]

The results of bacterial mutagenicity studies conducted with smoke condensate preparations and cytotoxicity assays using condensate or gas vapor phase preparations indicated no significant invert sugar-related effects on these *in vitro* endpoints.[121,122]

Inhalation exposure of rats to mainstream smoke from cigarettes containing various levels of invert sugar for 13 weeks did not result in any evidence of systemic toxicity. Assessment of peripheral blood or bone marrow samples for erythrocyte micronucleus formation during the 13-week inhalation study indicated no increased potential for clastogenic activity. Histopathologic changes were noted only in the respiratory tract tissues. Generally, the severity and incidence of the histopathologic changes were consistent with previous studies of cigarettes conducted at these smoke exposure levels.[123]

The smoke from the cigarette containing 100,000 ppm invert sugar appeared to be slightly more irritating in that male rats exposed to the smoke from the cigarettes containing 100,000 ppm invert sugar developed a slightly more severe degree of respiratory epithelial hyperplasia in nasal section 2, and also displayed an increased number of goblet cells in the bronchial epithelium. Changes in the respiratory tissues in the female rats exposed to smoke from the cigarettes containing 100,000 ppm invert sugar were comparable to control rat response. Exposure to smoke from cigarettes containing lower levels of invert sugar did not significantly increase the incidence or severity of response over control cigarette smoke. Examination of the respiratory tract following a non-smoking recovery period indicated a reversal of the histopathologic change. While some residual change was still evident in the nose of female rats exposed to smoke from cigarettes containing 100,000 ppm invert sugar at the end of the 6-week recovery period, numbers of goblet cells in the lung were no longer increased.[123]

The presence of the microscopic changes seen in the upper respiratory tract of male rats exposed to smoke from cigarettes containing 100,000 ppm invert sugar is consistent with the increased concentration of an irritant such as formaldehyde measured in the smoke atmosphere. The authors of the study concluded that the invert sugar no-observed-effect level (NOEL) was 50,000 ppm.[123]

The results of this evaluation of invert sugar, involving a review of current published information and internal studies, suggests that the addition of invert sugar as a cigarette ingredient below the maximum use level does not discernibly alter the biological effects normally associated with cigarette smoke exposure.

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