Worldwide Scientific Affairs

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From: Cathy Ellis

Subject: Review of "Tobacco smoke is a source of toxic glycation products," PNAS 94: 13915-13920 (1997)

Cerami *et al.* claim to have established that both aqueous tobacco extracts and tobacco smoke condensate contain certain substances they call "glycotoxins" which they allege will react with proteins and other cellular materials to form "advanced glycation end products" (AGEs). The authors claim that AGE levels are higher in smokers. AGE formation is purported to "contribute to the increased incidence of atherosclerosis and high prevalence of cancer in smokers."[1] Detailed reviews of this publication were received from Drs. Mingda Zhang (WSA Hong Kong), Ted Sanders (WSA Neuchatel), Walter Hempfling (R&D Richmond), and John Paine (R&D Richmond). An executive summary is provided here.

•Other sources of "glycation products"

"Advanced glycation end products (AGEs) are reactive cross-linking moieties that form from the reaction of reducing sugars and the amino groups of proteins, lipids, and nucleic acids," as defined by Cerami *et. al.* The terms "AGE" and "glycotoxin" have been coined by the authors and are not well characterized or accepted terms. However, sugars and proteins, lipids and nucleic acids are prevalent in many foods and no attempt was made to control for dietary sources of "glycotoxins." Food intake is likely to provide at least 100 times more reducing sugars and proteins relative to tobacco.

•Lack of chemical plausibility

The reaction of reducing sugars with amines has been known for at least a hundred years and is not new information. This reaction, called the Maillard browning reaction, commonly occurs when food is cooked or baked. The products of the Maillard reaction undergo further chemical change and then condense to result in Amadori products which are high molecular weight polymers that are characterized by high insolubility and low reactivity. Therefore, the observations of the authors suggesting "these reactive species" are the result of some other process or chemical constituent.

The fact that the "AGE activity" can be selectively filtered out of smoke supports the conclusion that other substances are being measured in these studies. Reducing sugars and similar compounds in smoke would reside in the particulate phase and particulate phase components cannot be selectively removed. Only materials in the gas phase have the potential to be selectively filtered.

The "extremely labile" nature of the activity described by the authors provides additional evidence of implausibility. If tobacco were to contain substances or their precursors that were as unstable in water as those described by Cerami *et al.*, they wouldn't survive years of storage, tobacco processing and the combustion and distillation processes associated with smoke formation. Therefore, the chemical behavior