ASSESSMENT OF COTININE AS A BIOLOGIC MARKER FOR ETS EXPOSURE

It has been reported that cotinine, a substance converted from nicotine by the body, can be used as a biological marker to measure nonsmoker exposure to ETS.[1-2] These reports, however, assume a direct correlation between exposure to nicotine in the ambient air and the existence of cotinine in body fluids. However, research indicates that such a correlation does not exist, for a number of reasons.[3-12] For example, researchers have reported that individuals metabolize nicotine in different ways at different times and that elimination rates for cotinine vary among individuals. In addition, recent research indicates that diet may contribute to levels of nicotine and cotinine found in the body, thereby interfering with ambient air exposure levels.[13] Scientists have also noted that different laboratory methods of analysis may influence final recorded levels of cotinine.[14] And finally, because cotinine is a metabolite of a gas-phase constituent of ETS, nicotine, cotinine levels do not represent exposures to other constituents of ETS.

The published literature on possible nicotine-cotinine correlations indicates enormous variability between the two proposed ETS markers. For example, in a paper cited in the SAB Review Draft

in support of the use of cotinine as an ETS marker, the authors (Cummings et al.) wrote: "Within a given exposure level there was considerable variability in cotinine values. Cotinine was chosen as a biological marker of ETS exposure because it is specific to tobacco smoke. However, cotinine levels in body fluids may not only reflect environmental exposure to tobacco smoke, but also factors that influence uptake and metabolism of nicotine."[8] The authors concluded:

> The relatively modest correlation between reported ETS exposure and urinary cotinine indicated that other factors such as differing metabolic rates and body size may have a confounding effect on the relationship between cotinine levels and questionnaire measures of ETS exposure. In view of this finding, we would recommend against using cotinine levels as a strictly quantitative indicator of ETS.

Similarly, research in 1985 by Johnson and colleagues indicated that: "[D]espite an identical exposure rate, considerable interindividual variability of subsequent nicotine and cotinine levels in saliva, plasma and 24-h urine were observed."[10]

Haley and co-authors reported in 1989 that the results of their study supported the concept that "cotinine elimination can be more rapid in smokers than in nonsmokers who are exposed to ETS."[7] They also noted that "differences in the mode of uptake and absorption of nicotine and possible differences in nicotine

metabolism may play roles in the clearance rate differences between smokers and nonsmokers."

In 1990, Japanese researchers examined the relationship between nicotine and cotinine levels in plasma and urine.[4] The results of their study indicated no consistent correlation among the four exposure markers for ETS, i.e., no consistent association between nicotine levels in plasma and urine with cotinine levels in plasma and urine.

In a commentary published in 1989, Jeffrey Idle of the Department of Pharmacological Sciences at the University of Newcastle in the United Kingdom wrote:[5]

> My own dissatisfaction with indiscriminate use of cotinine as a dosimeter of tobacco smoke arises from a trade-off of knowledge for convenience . . . [T]he extent of intersubject variability in human disposition of nicotine and its metabolites is both nebulous and poorly understood. The complex of dynamic interactions which leads to a certain salivary or urinary concentration of cotinine at one point in time following exposure to a defined amount of airborne nicotine needs to be dissected . . . [S]ingle point cotinine concentrations can give no more than a clue to a past exposure to pyridine alkaloids of unknown amount, at an unspecified time, by an unknown route of entry and from unknown origins.

Curvall and co-workers, in a report published in 1989, wrote:[3]

> The estimation of nicotine intake from cotinine concentrations in body fluids is valid only if the metabolism of nicotine and the subsequent elimination of cotinine are independent of the dose. The pharmacokinetics of nicotine and cotinine have been evaluated in smokers and nonsmokers at concentrations usually achieved by smokers, and little is known about the kinetics of these compounds at concentrations found in nonsmokers exposed to environmental tobacco smoke nicotine . . . **the suitability of cotinine as a marker of environmental tobacco smoke nicotine exposure has only been evaluated in field studies; no data are available on the relationship between low dose nicotine intake and cotinine concentrations in nonsmokers.** [emphasis added]

Similarly, in 1991, Proctor and associates reported on correlations among salivary cotinine levels, salivary nicotine levels, observed number of cigarettes smoked, and ambient exposure to ETS.[15] Correlations, on balance, were so poor that the researchers remarked that "this raises doubt about the validity of salivary cotinine information at low levels and suggests that studies that have suggested large portions of the population are being exposed to ETS may be misleading (Repace and Lowrey 1985; Wells 1988)."

Another report by Proctor (1990) reached a similar conclusion.[16] He wrote:

> The data shows [sic] little correlation between number of cigarettes smoked during the sampling

period and salivary cotinine at t_2 or with a change in salivary cotinine t_2-t_1. Furthermore, there is little correlation between personal exposures to nicotine and salivary cotinine at t_2 or t_2-t_1.

Other reviewers, Gori and Mantel, observed the following:[17]

> Hopes have been placed on nicotine and its metabolite cotinine as possible markers of ETS intake and actual internal dose (Cummings et al., 1990; Jarvis, 1989; Coultas et al., 1987; Jarvis et al., 1985; Hoffmann et al., 1984). Unfortunately ETS-nicotine resides mostly in the gas phase and decays at rates quite different from other ETS components, to which it will have ratios that are variable in time and largely unpredictable (Tang et al., 1988). Plasma cotinine levels suffer from similar and other shortcomings, although they have been shown to correlate with self-reported exposure to ETS (Cummings et al., 1990; Jarvis, 1989). Reports also suggest that physiologic clearance of nicotine and cotinine at low plasma levels may proceed at much slower rates, likely because of slower release from preferential body compartments (Lewis et al., 1990). Until these low-level kinetics are better understood, low plasma levels of nicotine and cotinine are likely to lead to substantial overestimations of intake doses. As such, nicotine and cotinine may provide a dichotomous index of contemporary exposure, but they remain inadequate as quantitative estimators of exposure, actual ETS dose, or their variation over an individual's life.

In conclusion, <u>cotinine is not a reliable quantitative measure of ETS exposure</u>. This is because body fluid levels of cotinine cannot be attributed solely to nicotine in ETS, and

because body fluid levels of cotinine do not correlate well with actual ambient air exposures to ETS or with ETS constituents other than nicotine. At best, cotinine may be used as a qualitative marker of ambient nicotine exposures. Consequently, attributable risk and exposure models based upon cotinine are seriously compromised.

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