C. MARKETED TOBACCO PRODUCTS DELIVER PHARMACOLOGICALLY ACTIVE DOSES OF NICOTINE

Scientific studies demonstrate that tobacco products currently marketed in the United States contain and deliver sufficient levels of nicotine to produce pharmacological effects on the central nervous system.[124]

1. Amount of Nicotine Necessary to Produce a Physiological Response in the Central Nervous System

In a recent study, the minimal dose of nicotine that was calculated to produce pharmacological effects on the central nervous system in humans was 0.18 mg.[125] In another study, based on nicotine nasal sprays, the minimal pharmacological dose was reported to be 0.2 mg for the average adult.[126]

Changes in the electroencephalogram (EEG) of smokers, indicative of central nervous system effects of nicotine, have been seen with plasma nicotine increases of 10 ng/ml, an amount easily obtainable from one cigarette.[127] Other studies have shown that EEG effects emerge after the first puff of cigarette and become pronounced and statistically significant by

---

[124] *See:*
Armitage AK, Dollery CT, George CF, Houseman TH, Lewis PJ, Turner DH. Absorption and metabolism of nicotine from cigarettes. *British Medical Journal.* 1975;4:313-316.

Stepney, note 119, *supra.*

[125] Yanagita T, Kiyoshi A, Wakasa Y, Shimada A. Behavioral and biochemical analysis of the dependence properties of nicotine. *Advances in Pharmacological Sciences.* (1995) (in press).

[126] KA Perkins. Statement in support of presentation by Jack Henningfield, Ph.D., to FDA Drug Abuse Advisory Committee Meeting. August 2, 1994.

[127] Kadoya C, Domino EF, Matsuoka S. Relationship of electroencephalographic and cardiovascular changes to plasma nicotine levels in tobacco smokers. *Clin Pharmacol Ther.* 1994;55:370-377.

the fourth puff.[128]

Even a single U.S. cigarette delivers enough nicotine to cause EEG changes indicative of pharmacological effects on the central nervous system.[129]

---

[128] *See:*

Knott V. Neuroelectric correlates of smoking behavior. In: Adlkofer F, Thurau, eds. *Effects of Nicotine on Biological Systems Advances in Pharmacological Sciences.* Boston, MA: Birkhauser; 1991:491-500.

Knott V. Dynamic EEG changes during cigarette smoking. *Neuropsychobiology.* 1988;19:54-60.

Knott V. Effects of low-yield cigarettes on electroencephalographic dynamics. *Neuropsychobiology.* 1989;21:216-222.

[129] *See:*

Pickworth WB, Heishman SJ, Henningfield JE. Relationships between EEG and performance during nicotine withdrawal and administration. In: Domino EF, ed. *Brain Imaging of Nicotine and Tobacco Smoking.* Ann Arbor, MI: NPP Books; 1995:1-11.

Pritchard WS, Gilbert DG, Duke DW. Flexible effects of qualified cigarette-smoke delivery on EEG dimensional complexity. *Psychopharmacology.* 1993;113:95-102.

Robinson JH, Pritchard WS, Davis RA. Psychopharmacological effects of smoking a cigarette with typical 'tar' and carbon monoxide yields but minimal nicotine. *Psychopharmacology.* 1992;108:466-472.

2. Nicotine Delivery From Currently Marketed Tobacco Products

a. Laboratory Studies

Currently marketed cigarettes contain, on average, 8 to 9 mg of nicotine in the tobacco rod.[130] FDA laboratory analysis demonstrates that currently marketed smokeless tobacco products contain between 8.8 and 26.4 mg of nicotine, per 2-gram sample of a typical "pinch."[131]

Currently marketed cigarettes typically deliver about 1 mg of nicotine to the bloodstream of smokers, with individual intake ranging from 0.3 to 3.2 mg of nicotine per cigarette.[132] Even members of the tobacco industry appear to agree that current cigarettes provide a pharmacologically active dose of nicotine. A senior industry researcher summarizing the views of industry scientists at a 1972 conference said that "[t]he physiological response to nicotine can be readily elicited by cigarettes delivering in the range of 1 mg of nicotine."[133]

Several studies reveal that with regular use throughout the day, the levels of nicotine

---

[130] *See* Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction. *N Engl J Med.* 1994;331:123-125.

[131] U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Drug Analysis Laboratory. *Study of Smokeless Tobacco Products: pH and Free Base Nicotine*. November 4, 1994, memorandum from Henry Drew, Chief, Drug Monitoring Branch, to Elizabeth Berbakos, Office of the Commissioner, FDA, and Frederick L. Fricke, FDA.

[132] Benowitz, note 130, *supra.*

[133] Dunn WL. Motives and incentives in cigarette smoking. Summary of CTR-sponsored conference in St. Martin. 1972. Philip Morris Research Center, Richmond, VA. (Summary of January 1972 St. Martin Conference referred to in preface of Dunn WL, ed. *Smoking Behavior: Motives and Incentives.* Washington, DC: VH Winston & Sons; 1973).

in the blood of smokeless tobacco users are similar to those observed in cigarette smokers.[134] In one study, the nicotine blood levels during ad libitum use of oral snuff (avg. 15.6 gm/day) or chewing tobacco (avg. 72.9 gm/day) were similar to those observed with cigarette smokers (avg. 36.4 cigarettes/day). In addition, the total daily levels of cotinine produced by various marketed tobacco products were similar, averaging 48.5, 48.25, and 46.17 μmol/L/hr for oral snuff, chewing tobacco, and cigarette tobacco, respectively.[135]

It has been shown that a single U.S. cigarette boosts plasma nicotine to as much as 23 ng/ml.[136] It also has been shown that a single "pinch" of smokeless tobacco produces peak plasma nicotine concentrations as high as 33 ng/ml and 21 ng/ml for oral snuff and chewing tobacco, respectively.[137]

b. The Federal Trade Commission Method

Another method to gauge nicotine delivery from cigarettes is based on levels published by the Federal Trade Commission (FTC). According to the FTC machine tests, the

---

[134] *See:*
Benowitz NL, Porchet HP, Sheiner L, Jacob P. Nicotine absorption and cardiovascular effects with smokeless tobacco use: comparison with cigarettes and nicotine gum. *Clin Pharmacol Ther.* 1988;44:23-28.

Holm H, Jarvis MJ, Russell MAH, Feyerabend C. Nicotine intake and dependence in Swedish snuff takers. *Psychopharmacology.* 1992;108:507-511.

[135] Benowitz NL, Jacob P, Yu L. Daily use of smokeless tobacco: systemic effects. *Ann Int Med.* 1989;111:112-116.

[136] *See* Benowitz, note 134, *supra.*

[137] *Id.* at p. 25.

See also Gritz ER, Baer-Weiss V, Benowitz NL, Van Vunakis H, Jarvik ME. Plasma nicotine and cotinine concentrations in habitual smokeless tobacco users. *Clin Pharmacol Ther.* 1981;30(2):201-209.

mean nicotine yield for cigarettes on a sales-weighted basis in 1991 was 0.94 mg of nicotine. Individual yields ranged from 0.1 to 1.9 mg, with 95% of all cigarettes sold falling in the narrower range of 0.32 to 1.56 mg of nicotine.[138] FTC yields for individual brands do not predict actual nicotine intake. Each cigarette rod contains significantly more nicotine than the amount "inhaled" by the smoking machine. Consequently, smokers may absorb more nicotine than the FTC machine, depending on the number and intensity of the puffs they take and whether their lips or fingers block the ventilation holes that can dilute the smoke from "low tar" and "ultra low tar" cigarettes.[139] Whether the tar and nicotine levels measured by the FTC test provide appropriate and useful information to smokers was the subject of a December 5-6, 1994, conference held by the National Cancer Institute at the request of the FTC and the then chairman of the Subcommittee on Health and the Environment of the House Committee on Energy and Commerce. The conferees concluded, among other things, that "actual human smoking behavior is characterized by wide variations in smoking patterns which result in wide variations in tar and nicotine exposure. Smokers who switch to lower tar and nicotine cigarettes frequently change their smoking behavior which may negate potential health benefits."[140]

---

[138] U.S. Federal Trade Commission. *Tar, Nicotine, and Nicotine/Tar Ratios by Year* (Weighted by Sales). U.S. Department of Commerce. 1994.

[139] Mueller M. Overview of the 1980-1994 Research Findings Relating to the Standard FTC Test Method For Cigarette Smoking (and studies cited therein). Prepared by ROW Sciences, Inc. for the National Cancer Institute Conference on the FTC Test Method for Determining Tar, Nicotine, and Carbon Monoxide Levels in Cigarettes, December 5-6, 1994. Smoking and Tobacco Control Program, National Cancer Institute. Bethesda, MD.

[140] Ad Hoc Committee of the President's Cancer Panel. Statement from the Ad Hoc Committee of the President's Cancer Panel to Consider the FTC Test Method for Determining Tar, Nicotine, and Carbon Monoxide Levels in Cigarettes. December 6, 1994.

It has been shown, for example, that smokers who switch to cigarettes with lower nicotine yields "compensate" by smoking the lower-nicotine cigarette more intensely and that the published FTC nicotine yield is not a good predictor of the amount of nicotine absorbed by smokers.[141] One study demonstrated that the actual intake of nicotine by smokers falls within a much narrower range than the published yields would suggest, and that the nicotine yield figures at the "low-yield" end of the spectrum significantly underestimate true rates of nicotine absorption.[142] This study found that while FTC nicotine yields in tested cigarettes ranged from 0.1 to 1.6 mg, actual nicotine intake by smokers ranged from 0.75 to 1.25 mg/cigarette. The study further confirms that U.S. cigarettes actually deliver in the range of 1.0 mg per cigarette.

To summarize, multiple studies show that marketed cigarettes and smokeless tobacco products deliver, on average, about 1 mg of nicotine.[143] Additionally, studies show that the

---

[141] *See:*

Benowitz NL, Hall SM, Herning RI, Jacob P III, Jones RT, Osman AL. Smokers of low-yield cigarettes do not consume less nicotine. *N Engl J Med.* 1983;309(3):139-142.

Kozlowski LT, Frecker RC, Khouw V, Pope MA. The misuse of "less-hazardous" cigarettes and its detection: hole-blocking of ventilated filters. *Amer J Public Health.* 1980;70(11):1202-1203.

Herning RI, Jones RT, Benowitz NL, Mines AH. How a cigarette is smoked determines blood nicotine levels. *Clin Pharm Ther.* 1983;33:84-90.

Herning RI, Jones RT, Bachman J, Mines AH. Puff volume increases when low-nicotine cigarettes are smoked. *Br Med J.* 1981;283:187-189.

[142] Gori GB, Lynch CJ. Analytical cigarette yields as predictors of smoke bioavailability. *Regulatory Toxicology and Pharmacology.* 1985;5:314-326.

[143] *See:*

Benowitz NL, Jacob P. Daily intake of nicotine during cigarette smoking. *Clin Pharmacol Ther* 1984;35(4):499-504.

Benowitz NL, Jacob P, Yu L. Daily use of smokeless tobacco: systemic effects. *Ann of Int*

amount of nicotine necessary to have pharmacological effects is much lower, in the range 0.2 mg.[144] Thus, currently marketed cigarettes and smokeless tobacco products deliver pharmacologically active doses of nicotine.

---

*Med.*1989;111:112-116.

Benowitz, note 134, *supra.*

Gori et al, note 142, *supra.*

[144] *See* Perkins, note 126, *supra.*