DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 95N–0253J]

Analysis Regarding The Food and Drug Administration's Jurisdiction Over Nicotine-Containing Cigarettes and Smokeless Tobacco Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; analysis regarding agency jurisdiction.

SUMMARY: The Food and Drug Administration (FDA) is publishing a document entitled ''Nicotine In Cigarettes And Smokeless Tobacco Products Is A Drug And These Products Are Nicotine Delivery Devices Under the Federal Food, Drug, and Cosmetic Act,'' and announcing the availability of appendices to this document. FDA has conducted an extensive investigation and has engaged in comprehensive analysis regarding the agency's jurisdiction over nicotine-containing cigarettes and smokeless tobacco products. The results of that inquiry and analysis support a finding at this time that nicotine in cigarettes and smokeless tobacco is a drug, and that these products are drug delivery devices within the meaning of the Federal Food, Drug, and Cosmetic Act. Nonetheless, because the agency recognizes the unique importance of the jurisdictional issue as well as the factual justification for any proposed rule in this area, the agency invites comment on these matters. Comments submitted will receive full and serious consideration.

DATES: Written comments by November 9, 1995.

ADDRESSES: ''Nicotine In Cigarettes And Smokeless Tobacco Products Is A Drug And These Products Are Nicotine Delivery Devices Under the Federal Food, Drug, and Cosmetic Act'' and its appendices may be purchased from Superintendent of Documents, U.S. Government Printing Office (GPO), Washington, DC 20402, 202–783–3238. ''Nicotine In Cigarettes And Smokeless Tobacco Products Is A Drug And These Products Are Nicotine Delivery Devices Under the Federal Food, Drug, and Cosmetic Act'' and its appendices are available for public examination in the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857, between 9 a.m. and 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT: Philip L. Chao, Office of Policy (HF–23), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–3380

SUPPLEMENTARY INFORMATION: The appendices referred to in the document entitled ''Nicotine In Cigarettes And Smokeless Tobacco Products Is A Drug And These Products Are Nicotine Delivery Devices Under the Federal Food, Drug, and Cosmetic Act'' are available from GPO (address above).

Elsewhere in this issue of the **Federal Register**, the agency is publishing a proposed regulation of nicotine-containing cigarettes and smokeless tobacco products. The agency recognizes the unique importance of the jurisdictional issue underlying this regulation as well as the factual justification for any proposed rule in this area. The agency invites comments on these matters. Comments submitted will receive full and serious consideration.

The text of ''Nicotine In Cigarettes And Smokeless Tobacco Products Is A Drug And These Products Are Nicotine Delivery Devices Under the Federal Food, Drug, and Cosmetic Act'' follows:

BILLING CODE 4160–01–F

Nicotine In Cigarettes And Smokeless Tobacco Products Is A Drug And These Products Are Nicotine Delivery Devices Under The Federal Food, Drug, And Cosmetic Act

U. S. Food and Drug Administration
Department of Health and Human Services
August, 1995

PREFACE

The Food and Drug Administration (FDA) has conducted an extensive investigation and has engaged in comprehensive legal analysis regarding the agency's jurisdiction over nicotine-containing cigarettes and smokeless tobacco products. The results of that inquiry and analysis support a finding at this time that nicotine in cigarettes and smokeless tobacco products is a drug, and that these products are drug delivery devices within the meaning of the Food, Drug, and Cosmetic Act. Nonetheless, because the agency recognizes the unique importance of the jurisdictional issue as well as the factual justification for any proposed rule in this area, the agency invites comment on these matters. Comments submitted will receive full and serious consideration.

Elsewhere in the same issue of the Federal Register in which this document is published, the agency is issuing a proposed regulation of nicotine-containing cigarettes and smokeless tobacco products under the restricted device provisions of the Act. Comments should be sent to FDA's Dockets Management Branch and identified with the docket number 95N-0253J. Comments should be submitted by the date identified in the Federal Register.

Traditionally, the FDA has initiated enforcement actions in cases where the agency determines that a product is a drug or a delivery device. Because the agency has elected to embark on this initiative through rulemaking, no enforcement action will be brought pending completion of that process.

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INTRODUCTION

Part One of this document (Legal Analysis of Jurisdiction over Tobacco Products) consists of three main sections. Section I demonstrates that nicotine's addictive and other pharmacological properties are effects on the "structure or any function of the body" within the meaning of the Act's definition of a drug. Section II demonstrates that tobacco manufacturers intend their products to have these effects within the meaning of the Act because: these effects are widely known and foreseeable to the industry; most consumers use tobacco products to obtain these effects; and tobacco manufacturers understand that consumers use tobacco products to obtain nicotine's pharmacologic effects and design their products to be used for these effects. Section III explains why regulation of cigarettes and smokeless tobacco products as devices is most appropriate at this time.

Part Two of this document (Findings) consists of two main sections. Section I presents the scientific evidence of nicotine's addictive and other pharmacological effects. This section also explains how marketed tobacco products deliver pharmacologically active doses of nicotine, and how consumers use these products to obtain various drug effects. Section II describes the statements, extensive research, and other actions by tobacco manufacturers regarding nicotine's pharmacological effects. This section identifies the industry's numerous acknowledgments that nicotine in tobacco acts as a drug and is addictive, and the industry's extensive research on nicotine's drug effects on the body. Section II also describes the considerable industry research on supplying sufficient nicotine to provide "satisfaction," determining the minimum and maximum dose of nicotine required by consumers, and assessing how consumers "compensate" to achieve an adequate dose of

nicotine.

Section II provides further evidence that manufacturers intend to market these products for their pharmacological effects, including explanations of the industry's: product development research to ensure that their products deliver doses of nicotine adequate to achieve pharmacological effects; manipulation and control of nicotine in marketed products; development of nicotine substitutes and alternative products that provide nicotine's drug effects; knowledge that nicotine's sensory effects are secondary to its pharmacological effects; and failure to remove nicotine from tobacco despite the available technology to do so.

Part Three of this document (Regulatory Objectives) summarizes FDA's objectives in regulating cigarettes and smokeless tobacco products. This section explains why, despite the significant public health problem caused by cigarettes and smokeless tobacco products, it would not be appropriate to remove them from the market because approximately 40 million Americans are addicted to these products. The section summarizes the evidence that almost all tobacco use begins during childhood or adolescence, and that the prevalence of tobacco use by children and adolescents is increasing. Therefore, the goal of FDA's regulatory action will be to reduce tobacco use by children and teenagers and prevent future generations from becoming addicted to nicotine-containing tobacco products.

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INTRODUCTION AND SUMMARY

FDA has jurisdiction over consumer products, including foods, drugs, medical devices, biologics, and cosmetics, under the Federal Food, Drug, and Cosmetic Act (FDCA or the Act), 21 U.S.C. §§ 301-394, a statute enacted to "safeguard the public health" and to "protect consumer welfare." H.R. Rep. No. 2139, 75th Cong. 3d Sess. 1-2 (1938).

The Act defines "drug" and "device" in a parallel manner. The term "drug" is defined, in relevant part, as an article "intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease" or "intended to affect the structure or any function of the body." 21 U.S.C. § 321(g)(1)(B), (C). The term "device" is defined as an instrument or other similar article "intended for use in the cure, mitigation, treatment or prevention of disease" or "intended to affect the structure or any function of the body." 21 U.S.C. § 321(h)(2), (3). These definitions are broad in scope and encompass a range of products wider than those ordinarily thought of as drugs or medical devices. Indeed, FDA has regulated such diverse, non-therapeutic products as narcotics without medical claims and tanning booths pursuant to these definitions. The question of whether a product is a drug or device is one that "the FDA has jurisdiction to decide with administrative finality, subject to the types of judicial review provided [in the FDCA]." Weinberger v. Bentex Pharmaceuticals, Inc., 412 U.S. 645, 653 (1973); see id. at 652-54; CIBA Corp. v. Weinberger, 412 U.S. 640, 643-44 (1973); see also Biotics Research Corp. v. Heckler, 710 F.2d 1375, 1377 (9th Cir. 1983).

Under the Act, FDA has jurisdiction over nicotine-containing cigarettes and smokeless tobacco products (hereafter "cigarettes and smokeless tobacco products") if they are intended to treat a disease or to affect the structure or any function of the body. As set forth in greater

detail below, the evidence now available to the agency demonstrates that cigarettes and smokeless tobacco products fall well within the definitions of drug and device.[1] It is well established that nicotine in tobacco is highly addictive, causes other psychoactive effects, such as relaxation and stimulation, and affects weight regulation. These responses to nicotine are effects on the structure or function of the body within the meaning of the Act.

The evidence before the agency also demonstrates that manufacturers intend to market and distribute products that affect the structure or function of the body within the meaning of the Act. Under the Act, Agency regulations, well-established case law, and longstanding Agency practice, discussed in detail below, "intended for use" and "intended to affect" can be demonstrated by evidence that: drug-like (pharmacological) effects in a large proportion of consumers are foreseeable by a reasonable manufacturer; consumers use the product predominantly and even nearly exclusively for its significant pharmacological effects; or manufacturers actually know that the product will be used for its significant pharmacological effects and have taken steps to encourage such use. In determining the intended use of a product, all relevant evidence may be considered, including the product's effect on consumers, consumer behavior and statements regarding the product, manufacturers' conduct and statements, results of scientific studies, and the other circumstances surrounding the distribution of the product.

In 1988, the U. S. Surgeon General issued a report formally recognizing that nicotine in cigarettes causes addiction. He had made a similar finding for smokeless tobacco products

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[1] The quality, quantity, and scope of the evidence available to FDA today is far greater than any other time when FDA has considered regulation of cigarettes and smokeless tobacco products. *See* LEGAL ANALYSIS § I.B.1., *infra,* p. 22.

in 1986. Today, nearly every major public health organization in this country and many experts who consult for the tobacco companies consider tobacco products containing nicotine to be addictive. In fact, recent major studies show that 75% to 90% of frequent smokers of tobacco are addicted. Thus, manufacturers of these products can reasonably be expected to foresee that their products are likely to lead to addiction in a large proportion of consumers.

This evidence also demonstrates that the vast majority of smokers and many smokeless tobacco consumers, because they are addicted to nicotine, use cigarettes and smokeless tobacco to satisfy nicotine dependence. Many of these consumers also use these products to affect mood and to control weight. Consumers use cigarettes predominantly and even "nearly exclusively" for their pharmacological effects.

Finally, internal tobacco industry documents demonstrate the industry's longstanding knowledge of and extensive research on the significant addictive and pharmacological effects of nicotine. Moreover, manufacturers of tobacco products have conducted product development research regarding the levels of nicotine necessary to produce pharmacological effects in tobacco users and also on methods of manipulating the amount of nicotine delivered by cigarettes. FDA's investigation has revealed that tobacco manufacturers actively control the amount and rate at which nicotine from marketed cigarettes and smokeless tobacco is delivered to consumers. Smokeless tobacco manufacturers both manipulate the amount of nicotine delivered by their products and promote the graduation of smokeless tobacco consumers from the lowest to the highest nicotine products, demonstrating an intention to facilitate nicotine dependence.

In summary, the evidence before the agency demonstrates that cigarettes and

smokeless tobacco products are intended to affect the structure and function of the body. Accordingly, the record[1a] before the agency demonstrates that cigarettes and smokeless tobacco products are drug delivery systems whose purpose is to deliver nicotine, a drug, and, hence, are devices under the Act. Given the current evidence, the nature of the products, and the nature of the regulatory framework, cigarettes and smokeless tobacco products should be regulated as devices under the Federal Food, Drug, and Cosmetic Act.

[1a]The phrase "record" as used throughout this document is not used as a term of art, but is used instead to refer to the accumulation of evidence gathered during FDA's investigation.

I. CIGARETTES AND SMOKELESS TOBACCO PRODUCTS "AFFECT THE STRUCTURE OR ANY FUNCTION OF THE BODY" BECAUSE THEY HAVE PHARMACOLOGICAL EFFECTS AND LEAD TO ADDICTION

The definition of drug in the Food and Drugs Act of 1906 included only articles "intended to be used for the cure, mitigation, or prevention of disease." Pub. L. No. 59-384, 34 Stat. 768 § 6. Congress added section 201(g)(1)(C)[2] when it enacted the Federal Food, Drug, and Cosmetic Act of 1938 in order to expand the reach of the drug definition to encompass products that escaped regulation under the 1906 act. Section 201(g)(1)(C) and the parallel section 201(h)(3), governing devices, reach products that do not have therapeutic uses but have, or are promoted as having, significant pharmacological or physiological effects. As House Report 2139 explained:

> *[t]he definition of drug is expanded to include . . . articles other than food intended to affect the structure or any function of the body of man or other animals. These expansions are needed to give jurisdiction over a great number of drugs which are not amenable to control under the present law.*

H.R. Rep. No. 2139 at 3, reprinted in 6 Legislative History 300, 302 (emphasis added). The principal example given in the legislative history of products "intended to affect the structure or any function of the body" is weight management products. The "structure or any function" language was needed because obesity and extreme thinness were not considered diseases. Congress was concerned with both the egregious nature of the claims for some of these products as well as the health risks associated with their use. See 78 Cong. Rec. 8960 (73d Cong., 2d Sess., May 16, 1934) (prepared statement of Senator Copeland), reprinted in 2 Legislative History at 831.

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[2] Section 201 of the Federal Food, Drug, and Cosmetic Act is now codified at 21 U.S.C. § 321.

While Congress' primary focus in 1938 was on products intended for weight management, it adopted language that included all products that affect the structure or function of the body. This expansion of the drug definition was "needed to protect the consumer . . . against a multiplicity of abuses not subject to the [1906 act]." S. Rep. No. 646, 74th Cong. 1st Sess. 1, reprinted in 4 Legislative History at 93. As one court explained:

> *The legislative history of the 1938 Act discloses that . . . the law which broadened the drug definition was enacted in part, and perhaps in important part, to control fraudulent remedies for obesity and leanness. But it also discloses that the expansion of the drug definition was not aimed solely at these remedies. They were merely illustrative of a comprehensive class of preparations which were intended to affect the structure or function of the body to which the legislation was directed.*

United States v. Article Consisting of 36 Boxes . . . "Lineaway, Temporary Wrinkle Smoother", 284 F. Supp. 107, 110 (D. Del. 1968), aff'd, 415 F.2d 369 (3d Cir. 1969) (emphasis added) (citations omitted).

Consistent with the statutory language and Congress' intent to insure that FDA has the authority to regulate products with non-therapeutic, but pharmacological effects, FDA has interpreted the provisions to encompass products that intrinsically have pharmacological or physiological effects, even though they are not promoted for therapeutic purposes. Examples of such products are topical hormones, sunscreens, and tanning booths. See Appendix to Legal Analysis. Judicial constructions of sections 201(g)(1)(C) and 201(h)(3) are consistent with this interpretation. See, e.g., E.R. Squibb & Sons, Inc. v. Bowen, 870 F.2d 678, 683 (D.C. Cir. 1989) (summarizing cases); United States v. Undetermined Quantities of Cal-Ban 3000, 776 F. Supp. 249, 253 (E.D.N.C. 1991) ("[T]he term 'drug' should be interpreted broadly and not limited to only products which are commonly known as drugs.").

Courts have been careful to distinguish between remote physical effects which arguably might fall within the literal language of section 201(g)(1)(C) or section 201(h)(3) and significant effects on structure or function which clearly fall within the provisions' ambit. "[R]emote physical effect[s] on the body" are not covered by the structure or function provision. E.R. Squibb & Sons, 870 F.2d at 682. On the other hand, products intended to prevent pregnancy, thus affecting the reproductive function of the human body, fall within that definition. Id. at 682-83.

For example, a product intended to reduce the number of bacteria in an animal's digestive system and oral cavity is a drug within the meaning of section 201(g)(1)(C) because it "was intended to alter a function of the animal's body." United States v. Undetermined Quantities . . . "Pet Smellfree", 22 F.3d 235, 240 (10th Cir. 1994). Similarly, liquid solutions intended to cause hair growth and prevent hair loss are drugs within the meaning of section 201(g)(1)(C) because the hair growth process is a function of the human body. United States v. Kasz Enterprises, Inc., 855 F. Supp. 534, 540 (D.R.I. 1994), judgment modified on other grounds, 862 F. Supp. 717 (D.R.I. 1994). Likewise, an apparatus containing oxygen that is intended to improve athletic performance by increasing a tired athlete's intake of oxygen falls within sections 201(g)(1)(C) and 201(h)(3) because enhanced oxygen absorption alters a bodily structure or function. United States v. Eighteen Units, More or Less Of An Article of Drug . . . "SPORTS OXYGEN . . .", Civ. No. 89-2085 (D.N.J. October 27, 1992), reprinted in Food, Drug, and Cosmetic Act Judicial Record, 1991-92 115. Cocaine and similar substances with parallel addictive and psychoactive effects also fall within the drug definition because

they "affect the structure or any function of the body."[3]

In each of these cases, a significant pharmacological effect on the body can bring a substance within the drug definition, even when the product has no therapeutic effect. On numerous other occasions, the Agency has reached similar conclusions and has taken regulatory action. See Appendix to Legal Analysis for examples. As is discussed at p. 22, et seq., it is now widely accepted that nicotine has pharmacological effects on both the structure and function of the central nervous system, particularly the brain. Addiction is a direct result of nicotine's effects on the structure and function of the body. Id. Based on the record before the agency, cigarettes and smokeless tobacco products "affect the structure or any function of the body" within the meaning of sections 201(g)(1)(C) and 201(h)(3).

[3] In fact, the Controlled Substances Act, 21 U.S.C. §§ 801-904, which prohibits the sale of drugs such as cocaine, defines "drug" by reference to section 201(g)(1) of the FDCA. 21 U.S.C. § 802(12).

II. TOBACCO MANUFACTURERS "INTEND" THAT THEIR PRODUCTS HAVE ADDICTIVE AND SIGNIFICANT PHARMACOLOGICAL EFFECTS.

The FDCA, FDA's regulations, and judicial decisions interpreting the Act and analogous provisions in other public welfare statutes all demonstrate that "intended to" and "intended for," as used in the Act, denote objective intent, as that term has become commonly understood by the courts. Objective intent may be determined by what a reasonable person would understand in the circumstances presented, or whether a "reasonable person would believe" that the defendant's conduct would lead to certain events. See, e.g, United States v. Articles of Banned Hazardous Substances . . . Baby Rattles, 614 F. Supp. 226, 231 (E.D.N.Y. 1985) ("[t]he only rational interpretation of the word 'intended' in the statute calls for an objective test of intent: whether a reasonable person would believe that the object is a toy"); W. Page Keeton et al., Prosser and Keeton on the Law of Torts § 8, at 36 (5th ed. 1984) ("relying on circumstantial evidence, [one] may infer that the actor's state of mind was the same as a reasonable person's state of mind would have been").

The courts have also described objective intent in terms of foreseeability. For example, in United States v. Focht, the Third Circuit held that the intent requirement in the "intended to produce [banned] fireworks" language of the regulations implementing the Federal Hazardous Substance Act (FHSA) could be satisfied by a demonstration that it was "foreseeable" that the components sold by the defendant would be used to build banned products. 882 F.2d 55, 59-60 (3d Cir. 1989); see 15 U.S.C. § 1261(q). Similarly, in defining discriminatory intent in a voting rights case, the Fifth Circuit held that "[o]bjective intent . . . presumes that a person intends the natural and foreseeable consequences of his voluntary

actions." Lee v. Lee County Bd. of Ed., 639 F.2d 1243, 1267 (5th Cir. 1981).[4]

Subsection A, infra, demonstrates that an objective intent standard is the appropriate standard under the FDCA. The evidence in subsection B, infra, demonstrates that tobacco manufacturers "intend" cigarettes and smokeless tobacco products to affect the structure or any function of the body within the meaning of the FDCA.

A. OBJECTIVE INTENT IS THE APPROPRIATE STANDARD.

The FDCA is a consumer protection statute which has as its explicit purpose the "prohibit[ion of] the movement in interstate commerce of adulterated and misbranded foods, drugs, devices, and cosmetics." Pub. L. No. 75-717, 75th Cong. 3d. Sess. (1938); see also H.R. Rep. No. 2139 at 1-2, reprinted in 6 Legislative History at 300-01 ("this act seeks to set up effective provisions against abuses of consumer welfare"; "the old law . . . contains serious loopholes [and] is not sufficiently broad in its scope to meet the requirements of consumer protection under modern conditions"; the 1938 Act "amplifies and strengthens the provisions [of the 1906 act] designed to safeguard the public health and prevent deception, and it extends the scope of the old law to include . . . certain drugs that now escape regulation").

Given the Act's focus on consumer welfare and public health protection, interpreting

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[4] Subjective intent, on the other hand, considers the actual state of mind of the responsible actor. *See, e.g.*, Ellington v. Metropolitan Life Ins. Co., 696 F. Supp. 1237, 1242 (S.D. Ind. 1988) (a subjective intent test requires a determination that the defendant actually foresaw the result of his conduct and persisted nonetheless). This standard, which focuses on the actor's actual desires and knowledge, has been applied in certain areas of criminal law when the critical issue is the culpability of a particular actor. *See, e.g.*, Morisette v. United States, 342 U.S. 246, 250-52 (1952). It is not used as a standard of proof for intent in public health and welfare statutes such as the FDCA.

the phrases "intended for use" and "intended to affect" to require a showing of subjective intent -- which would limit the relevant evidence to what is in the mind of the manufacturer or vendor as shown by express representations, promotional claims, or otherwise -- would frustrate those legislative policy goals. As one court found, in determining that an objective intent standard is appropriate in construing a consumer protection statute: "[t]he subjective interpretation of intent urged by claimant could seriously diminish the effectiveness of FHSA [the Federal Hazardous Substances Act] because it would enable a manufacturer to introduce dangerous articles into commerce on the unreasonable but good faith belief that the articles would not be used by children." Baby Rattles, 614 F. Supp. at 232. The court further noted that "the language of the FHSA . . . nowhere speaks specifically of the manufacturer's subjective intent," and that a subjective intent standard could not possibly comport with Congress' intent in enacting the FHSA. Id. 231-32. The same reasoning extends to the Federal Food, Drug, and Cosmetic Act. The language and purposes of the FDCA support an objective intent standard that allows consideration of information about the foreseeable uses of the product for pharmacological purposes, as well as any statements or actions by the vendor that might show the vendor's actual purpose in marketing a product, or refute the vendor's claims regarding the product's intended use.

Although the FDCA is not primarily a criminal statute designed to punish law breakers, it does include criminal penalties to enforce its provisions. See, e.g., 21 U.S.C. § 333. It is relevant that the Act imposes a strict liability standard that is applicable to criminal prosecutions and assesses criminal liability even where there is no evidence of actual knowledge of the alleged conduct on the part of the corporate defendant. 21 U.S.C. § 331;

see United States v. Dotterweich, 320 U.S. 277, 280-81 (1943); United States v. Park, 421 U.S. 658, 670-73 (1975); see also Smith v. California, 361 U.S. 147, 152 (1959) (some penal statutes "dispense with any element of knowledge on the part of the person charged, food and drug legislation being a principal example . . . . The usual rationale for such statutes is that the public interest in the purity of its food is so great as to warrant the imposition of the highest standard of care on distributors -- in fact an absolute standard which will not hear the distributor's plea as to the amount of care he has used.").

Moreover, FDA's regulations interpreting sections 201(g)(1) and 201(h), which were adopted after notice and comment rulemaking, and therefore have the force and effect of law, explicitly adopt an objective intent standard. Those regulations, which were originally promulgated in 1952, describe the evidence relevant to determining intent to include:

> *such [manufacturers' or vendors'] expressions or . . . by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such [manufacturers or vendors] or their representatives. It may be shown by the circumstances that the article is, with the knowledge of such [manufacturers or vendors] or their representative, offered and used for a purpose for which it is neither labeled nor advertised . . .*

21 C.F.R. § 201.128 (1994) (drugs) (emphasis added); see 21 C.F.R. § 801.4 (1994) (parallel provision for devices); see also 17 Fed. Reg. 6818 (July 24, 1952). Thus, under these regulations, evidence of objective intent is not limited to expressions in labeling or advertising, but may be based on the totality of the relevant evidence showing the seller's awareness of how its product is actually used and affects the structure or function of the body, regardless of how the product is labeled or advertised.

The foregoing interpretation of the statutory language is also consistent with FDA's

regulatory policy decisions and actions. As demonstrated in the Appendix to Legal Analysis, FDA has used both general knowledge and recognition of products' nature and effects, as well as their actual uses and effects, to determine whether products fall within the statutory definitions of drug or device.

FDA has used the known or inherent pharmacological effects of particular ingredients to determine that products are "intended to affect the structure or any function of the body," even where there are no public expressions by the seller that the product is to be used for those effects. See Appendix to Legal Analysis. For example, in the context of a proposed rule on vaginal products for over-the-counter use, the Agency stated:

> *If an active ingredient is present in a therapeutic concentration, the product is a drug, even if that product does not claim to produce the effect which will result from the action of the therapeutically effective ingredient.*

48 Fed. Reg. 46694, 46701 (October 13, 1983). In its tentative conclusion to comments on this issue, the Agency reiterated:

> *[t]he type and amount of ingredient(s) present in a product, even if that product does not make explicit drug claims, must be considered in determining its regulatory status. For example, the mere presence of a pharmacologically active ingredient could make a product a drug even in the absence of explicit drug claims. In these cases, the intended use would be implied because of the known or recognized drug effects of the ingredient (e.g., fluoride in a dentifrice).*

59 Fed. Reg. 5226, 5227 (February 3, 1994) (emphasis added).

Thus, products containing ingredients or components with known pharmacological effects, including fluoride and hormones, have -- on that basis alone and in the absence of express claims -- been determined to be "intended to affect the structure or function of the body" because they contained a pharmacologically active ingredient. See Appendix to Legal

Analysis. FDA has also regulated as devices products that affect the structure or function of the body, even when the vendor makes no claims regarding the products. For example, FDA regulates as devices noncorrective tinted contact lenses that are expressly promoted only for their cosmetic effect of enhancing eye color because they have physiological effects on the eye. See Appendix to Legal Analysis.

The courts have consistently held that the statutory language imposes an objective intent standard. United States v. Undetermined Quantities . . . "Pet Smellfree", 22 F.3d 235, 236, 239 (10th Cir. 1994) (referring to "objective intent" in the context of considering whether a product is a drug); United States v. Kasz Enterprises, Inc., 855 F. Supp. 534, 542 (D.R.I. 1994) ("it is the objective intent of the vendor, not the vendor's subjective explanations and disclaimers, which determines the intended use of a product") (emphasis added), judgment modified on other grounds, 862 F. Supp. 717 (D.R.I. 1994); Clinical Reference Laboratory v. Sullivan, 791 F. Supp. 1499, 1506 n.8 (D. Kan. 1992) ("intended use . . . depends upon the objective intent of the persons responsible for its labeling") (emphasis added), aff'd in relevant part, rev'd in part on other grounds sub nom., United States v. An Undetermined Number of Unlabeled Cases, 21 F.3d 1026 (10th Cir. 1994); United States v. Two Plastic Drums, 761 F. Supp. 70, 72 (C.D. Cal. 1991) ("In determining . . . intended use . . , the inquiry should focus on the vendor's objective intent") (emphasis added); United States v. Articles of Drug . . . Neptone, No. C-83-0864-EFL, CCH Food and Drug Reporter ¶ 38,240 at 39,294 (N.D. Cal. October 25, 1983) ("objective manifestations of intent are clearly sufficient").

The Environmental Protection Agency (EPA) and the Consumer Product Safety

Commission (CPSC) have also adopted an objective intent standard in construing similar provisions in the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and the Federal Hazardous Substances Act (FHSA), and courts have uniformly upheld those interpretations. See e.g., N. Jonas & Co. Inc. v. EPA, 666 F.2d 829, 833 (3d Cir. 1981); United States v. Focht, 882 F.2d 55, 58-60 (3d Cir. 1989); Baby Rattles, 614 F. Supp. at 231-32. Judicial constructions of those statutes demonstrate that evidence of actual consumer use, knowledge by the manufacturer of such actual use, general knowledge about the effectiveness of the product for a particular use, and other circumstances surrounding its distribution, can be used to determine the "intended use" of a product for purposes of a public welfare statute such as the FDCA.

In Jonas, the issue was whether "Scorch," a product labeled for swimming pool sanitation and maintenance, was a pesticide. The product's label contained a disclaimer stating: "Scorch is not to be used for daily disinfection or algae control of your pool." 666 F.2d at 831. The manufacturer contended that a product's intended use can be determined only from the company's express representations concerning the product. Id. at 832. EPA took the position that "intended use" should be based on the use to which a reasonable consumer would put the product based on "the collectivity of the circumstances." EPA also argued that "[t]he fact that the product may have other uses does not affect" whether it qualifies as a pesticide. Id. The court, relying in part on cases under the FDCA, agreed with EPA and held that the statutory phrase "intended use" refers to objective intent and, as a result, the manufacturer "intends those uses to which the reasonable consumer will put its products." Id. at 832-33.

In deciding whether sufficient evidence exists to support a finding of objective intent, the court in Jonas stated that "the inquiry cannot be restricted to a product's label and to the producer's representations." Id. at 833. Instead, the court determined that relevant evidence could come from, among other things, "general public knowledge" of the usefulness of similar products as pesticides, the "effectiveness" of the product for a pesticidal use (that is, its actual inherent effects), and the collectivity of all the circumstances. Id.

Similarly, in Baby Rattles, the court held that the phrase "any toy or other article intended for use by children" in 15 U.S.C. § 1261(f)(1)(D) requires application of an objective intent standard, and that this standard is met if evidence exists that "a reasonable person would believe that the object is a toy or article intended for use by children." 624 F. Supp. at 231. The court found that this standard was met with respect to a rattle marketed by the manufacturer as a "party favor" based on "evidence of its use as a toy and the common sense observation that children would be likely to use it as a toy." Id. at 231 n.9.

The court observed that even if it accepted the manufacturer's argument that the "intended use" language in the FHSA should be interpreted as requiring a subjective intent standard, such intent would have been established by evidence that the manufacturer knew that its rattles were used on babies' shoes and were given as gifts at baby showers: "[C]laimant could not possibly have ignored the possibility that children would use the rattles, regardless of whether he intended such use of the rattles and whether reasonably prudent parents would give such objects to their children." Id.

Finally, in Focht, component parts of fireworks sold by the Fochts were held to have been "intended to produce banned fireworks" under the FHSA, based on evidence that the

parts were likely to be used by consumers to make banned fireworks, and despite evidence that the components could also be used for numerous legal purposes. An expert testified at trial that 90% of consumers who purchased the components in question would use them to make illegal fireworks, and that, if the components were filled in the "traditional manner," they would contain over the legal limit of explosive. 882 F.2d at 59-60. The court held that "[i]ntended use . . . objectively defined, necessarily encompasses foreseeability" and that this testimony made it "foreseeable that the components in question will be used to build banned fireworks. Such knowledge must be attributed to the Fochts." Id. at 60. Accordingly, a finding that a product is intended to affect the structure or function of the body may be appropriately based on evidence that use of a product leading to such effects in a large proportion of consumers is foreseeable.

Objective intent may also be established by evidence, alone or in combination with other evidence, that consumers use a product for pharmacological purposes. See Action on Smoking and Health [ASH] v. Harris, 655 F.2d 236, 239 (D.C. Cir. 1980) (consumer use may be relevant source of evidence of intended use); National Nutritional Foods Assn [NNFA] v. Mathews, 557 F.2d 325, 333-34 (2d Cir. 1977) (product's use for therapeutic purposes was evidence of intended use); United States v. Two Plastic Drums, 761 F. Supp. 70, 72 (C.D. Cal. 1991) (consumer use is relevant to intended use); see also Medical Devices Amendments of 1976, H.R. Rep. 94-853, 94th Cong., 2d Sess. at 14 (1976) (in interpreting "intended for use" and "intended to affect," FDA "may consider the ultimate destination of a product . . . just as [it] may consider actual use of a product"); Sunscreen Drug Products for Over-the-Counter Human Use; Tentative Final Monograph; Proposed Rule, 58 Fed. Reg.

28194, 28204 (May 12, 1993) (objective evidence of intent may be derived from "the consumer's intent in using the product").

In ASH, the D.C. Circuit stated that "the near-exclusivity of consumer use of cigarettes with the intent 'to affect the structure or any function of the body of man,'" would be sufficient by itself to establish that cigarettes are drugs within the meaning of the FDCA. 655 F.2d at 240; see also NNFA, 557 F.2d at 336 (demonstration that high dosage vitamins were "taken 'almost exclusively' for therapeutic purposes" would show an objective intent that the products be used as drugs and be sufficient for a determination that the products are drugs within the FDCA's meaning).

Evidence of consumer use may also be used in combination with other evidence to establish intended use or intended effects. FDA has relied on evidence of consumer use to establish the intended use of a drug or device product, even though the extent of consumer use had not been quantified. For example, beginning in the early 1980's, FDA regulated as unapproved drugs imports of catha edulis, or "khat," a shrub whose leaves act as a stimulant narcotic that affects the central nervous system when chewed or used as tea, even though the Agency did not have any evidence that vendors represented the product as a stimulant. Instead, FDA relied on information about the product's use and effects from United Nations reports, and other sources of information that described international customs and practices related to the substance. See Appendix to Legal Analysis.

Similarly, physicians' use of a product to treat or diagnose patients or to affect the structure or function of patients' bodies may provide evidence of intended use. FDA has classified products as drugs or devices based on physician use of the product. For example,

FDA undertook an enforcement action against a metal tube containing a light bulb, round metal discs, and colored glass filters used by a medical practitioner in his office in the treatment of various eye malfunctions and conditions. A district court upheld the Agency's conclusion that this use made the tube a device, even though the practitioner made no claims for the product. United States v. An Article of Device . . . Labeled in Part: "Cameron Spitler Amblo-Syntonizer", 261 F. Supp. 243, 245 (D. Neb. 1966). In another example, FDA established a due diligence requirement regarding manufacturers' distribution of interferon, a biologic product composed of proteins. See 48 Fed. Reg. 52644 (Nov. 21, 1983). At the time, interferon could be used only for investigational purposes in laboratory animals and tests in vitro. However, interferon received wide media coverage as a potential "miracle cure" in the treatment of cancer and viral infections in humans. Because of its concern over diversion of interferon to unapproved uses, the Agency issued the notice to prevent use of interferon in humans.

Finally, a vendor's behavior or statements may also be used as evidence of objective intent. See, e.g. United States v. An Article . . . Consisting of 216 Cartoned Bottles . . . "Sudden Change", 409 F.2d 734, 739-741 (2d Cir. 1969) (lotion promoted on product box, leaflets, and advertising as providing a "face lift" is intended to affect the structure of the body and is a drug); "Pet Smellfree", 22 F.3d at 239-40 (compound labeled and marketed as eliminating odor from a pet's breath and waste material is intended to affect the animal's digestive and elimination functions and is a drug).

Awareness that a product will achieve pharmacological effects, actual use of the product for a pharmacological purpose, and the totality of circumstances surrounding

distribution of the product constitute "objective manifestations of intent [that] are clearly sufficient." Neptone, CCH Food and Drug Reporter at 39,294. Moreover, evidence that a manufacturer actually knows that its product is being widely used for pharmacological purposes, and has taken steps to facilitate that use, provides compelling evidence of "intended use."

As shown below, the evidence now available to FDA demonstrates that tobacco manufacturers "intend" that their products have addictive and pharmacological effects which make cigarettes and smokeless tobacco products drugs within the meaning of the Act.

B. THE EVIDENCE DEMONSTRATES INTENT TO AFFECT THE STRUCTURE OR FUNCTION OF THE BODY.

As demonstrated above, in order to establish that a product has an intended use that subjects it to FDA's jurisdiction, it is sufficient to demonstrate foreseeable drug uses or effects in a large proportion of users, predominant or "nearly exclusive" consumer use for drug effects, or the subjective intent of the manufacturer, as evidenced by behavior and statements, that the product be used as a drug. As shown below, the facts before the agency demonstrate, based on each of these three grounds, that tobacco products are intended to affect the structure or function of the body and are, therefore, "drugs" and "devices." Moreover, the combined evidence before the agency from all three categories plainly demonstrates that tobacco products are "drugs" and "devices" within the meaning of the Act.[5]

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[5] Since 1980, when the Agency last evaluated its legal authority to regulate cigarettes as drugs or devices and declined to do so, *see* Action on Smoking and Health [ASH] v. Harris, 655 F.2d 236 (1980), the evidence regarding intended use has changed dramatically. As discussed *infra*, since 1980, the Surgeon General of the United States and virtually every major public health organization have concluded that nicotine in tobacco products leads to addiction. Since that time, the Agency has also exercised

1. The Addictive, Psychoactive, and Other Pharmacological Effects of Nicotine Are Widely Known and Foreseeable by Any Reasonable Person in the Position of a Tobacco Manufacturer.

As summarized below, a large body of compelling and widely accepted scientific evidence now exists that establishes that nicotine is addictive. Nicotine's addictive properties and its other significant pharmacological effects are now so well documented and commonly understood that these effects on the structure or function of the body must be held to be foreseeable by any manufacturer of cigarettes or smokeless tobacco products that contain nicotine. Although the manufacturers' claimed purpose may be to provide "taste" or "smoking pleasure," manufacturers may nevertheless be held, under an objective intent standard, to intend the foreseeable consequences of consumers' use of nicotine-containing cigarettes and smokeless tobacco products.

a. Addictive Effects. Until the 1980's, nicotine was not widely appreciated to be an addictive drug.[6] Overwhelming scientific evidence and broad recognition that nicotine is an addictive or dependence-producing substance emerged in the 1980's. See p. 78. Almost all

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jurisdiction over alternative nicotine delivery systems such as "Favor," a plug impregnated with a nicotine solution inserted within a small tube corresponding in appearance to a conventional cigarette, and "Future Free," a roll-on transdermal applicator containing nicotine in the form of a liquified raw tobacco extract, nicotine gums, and nicotine transdermal patches. Finally, the Agency's investigation has identified a wealth of evidence consisting of industry statements, research and actions acknowledging nicotine's drug effects and the role of nicotine in the manufacture of cigarettes and smokeless tobacco. As the Court explicitly acknowledged in ASH, the FDCA "calls for case-by-case analysis," and an agency may "depart from its prior interpretations" so long as it "provide[s] a reasoned explanation for its action." 655 F.2d at 242 n. 10; *see also* Chevron, U.S.A., Inc. v. National Resources Defense Council, Inc. 467 U.S. 837, 842-845, (1984); Bell v. Goddard, 366 F. 2d 177, 181 (7th Cir. 1966) ("An interpretation of the statute prohibiting such new application of existing information would do violence to the paramount interest in protecting the public from unsafe drugs."). In this document, the Agency has provided such a reasoned explanation.

[6] While some evidence of the addictive nature of nicotine existed at the time FDA last considered the regulation of nicotine-containing cigarettes and smokeless tobacco products in the late 1970's, the evidence available to FDA since that time has grown exponentially. *See* FINDINGS § I.B.

the leading experts and public health organizations in the United States and in the international community, including the vast majority of scientists funded by the tobacco industry now recognize nicotine's addictive effects. In 1986, the Office of the U.S. Surgeon General published a finding that nicotine in smokeless tobacco is addictive. See p. 80. Two years later, the Surgeon General issued his landmark report concluding that: cigarettes and smokeless tobacco products are addicting; nicotine is the drug in tobacco that causes addiction; and the pharmacological and behavioral processes that cause tobacco addiction are similar to those that cause addiction to drugs such as heroin and cocaine. See p. 82.

Since 1980, nicotine has been recognized as addictive or dependence-producing[7] by the World Health Organization, the American Medical Association, the American Psychiatric Association, the American Psychological Association, the American Society of Addiction Medicine, the Royal Society of Canada, and the Medical Research Council in the United Kingdom. See p. 82. In a 1991 survey, the vast majority of scientists funded by the tobacco industry stated that they believe that cigarette smoking is addictive. See p. 83. Indeed, among the principal investigators of research projects funded by the tobacco industry in 1989, 83.3% strongly agreed and 15.3% agreed somewhat that cigarette smoking is addictive. See p. 83.

More recently, on August 2, 1994, FDA's Drug Abuse Advisory Committee concluded unanimously that cigarettes and other forms of tobacco are addicting and that nicotine is the drug in tobacco that causes addiction. See p. 83. The FDA Advisory Committee also

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[7] The terms "addictive" and "dependence-producing" are generally used interchangeably; both refer to the persistent and repetitive intake of psychoactive substances despite evidence of harm and a desire to stop using the substance. *See* p. 78. The terms are used interchangeably in this document.

concluded that all currently marketed cigarettes contained addicting levels of nicotine. Id.

Tobacco use is also recognized as an addiction in the leading psychiatric manuals defining mental illnesses. The two most widely used clinical definitions of addiction in the United States are those in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) and World Health Organization's International Classification of Diseases (ICD). Nicotine has been recognized as dependence-producing under the DSM criteria since 1980. The ICD has recognized tobacco as dependence-producing since 1992. See pp. 84-85.

The current, scientifically accepted method of identifying addictive substances relies on the knowledge that there is a pharmacologic basis to addiction. See p. 79. Addictive substances achieve their addictive effects by exerting psychoactive (mood-altering) effects, and by producing chemical reactions in the brain that motivate repeated, compulsive use of the substance. See pp. 79-80. These pharmacologic effects create psychological or physiological dependence in the user. Id. Nicotine has been shown in animal and human studies to be a powerful psychoactive agent and to produce effects in the brain that are characteristic of other addictive substances, such as heroin and cocaine. See p. 94 et seq. Nicotine has also been shown to act as a "positive reinforcer," perhaps the most important hallmark of an addictive substance. See p. 96.

Current, widely accepted definitions of substance addiction place primary emphasis on: compulsive, regular use of the substance; inability to stop using the substance despite a desire to quit and/or harmful consequences; and the existence of tolerance and/or withdrawal symptoms (physiologic dependence). See p. 84. Using the contemporary definition of

addiction, evidence from epidemiological studies has now established that many cigarette smokers and smokeless tobacco users are addicted to nicotine.

Numerous studies have documented the characteristics of addiction among cigarette and smokeless tobacco users. First, consumers use tobacco regularly and compulsively. For example, 87% of people who smoke cigarettes smoke every day. See p. 86. Nearly two-thirds of smokers need their first cigarette within the first half-hour after awakening. Id.

Second, the failure rate of people who attempt to stop or reduce their smoking is dramatic, even in the face of life-threatening, tobacco-related illnesses. See pp. 86-87. Each year, nearly 15 million people -- almost one-third of all smokers -- try to quit smoking in the United States. Only about 3% of would-be quitters achieve long-term success. Indeed, cigarettes and smokeless tobacco products may be the only elective consumer product that a majority of users want to quit using, but cannot. In response to the 1993 National Health Information Survey, 70% of current smokers reported that they would like to completely stop smoking cigarettes. See p. 87. Sixty-eight percent of smokeless tobacco users in one study reported an average of four previous unsuccessful attempts to quit using smokeless tobacco. See p. 91. Moreover, tobacco use persists despite harmful and often deadly consequences. In one survey, 90% of smokers agreed with the general proposition that smoking is harmful to health, 65% believed that smoking had already adversely affected their health, and 77% believed that they could avoid or decrease serious health problems by quitting smoking. See p. 87. Almost half of the smokers who have surgery for lung cancer resume smoking. See p. 87. Even when smokers have their larynxes removed, 40% try smoking again. See p. 87.

Third, consumers who abstain from tobacco products experience withdrawal symptoms and nicotine has been shown to produce tolerance (the lessening of the desired effect over time or the need for higher doses to produce the same effect) among tobacco users. See pp. 88, 92, 99. For example, abstinence from smoking is often accompanied by powerful cravings for a cigarette, and the range of other symptoms produced by abstinence can disrupt personal life. Id. Among smokeless tobacco users, one study showed that of users 10 to 22 years old who had tried to quit, 93% had suffered withdrawal symptoms. See p. 93.

Accordingly, nicotine satisfies the classic criteria for an addictive substance. In fact, major recent clinical studies have demonstrated that between 75% and 90% of frequent smokers, and more than one-third of smokeless tobacco users are addicted to tobacco. See pp. 91, 115 et seq.. Further, cigarette users themselves recognize that cigarettes are addictive. According to a national household survey conducted by the U.S. Department of Health and Human Services in 1991-92, 83% to 87% of cigarette smokers who smoke more than 26 cigarettes a day believe they are addicted. See p. 87.

The success of nicotine replacement therapies provides further evidence of nicotine's addictive qualities. Nicotine replacement therapies (nicotine gum and nicotine patches) have been shown to be effective in assisting dependent tobacco users to quit. See p. 88 et seq. Nicotine replacement could only significantly increase the success of smoking cessation efforts if nicotine dependence were the major factor preventing tobacco users from quitting. Id.

To summarize, the widely known, well-publicized evidence of the addictive nature of nicotine and the very high frequency of addiction among frequent smokers, ranging, in major

recent studies, from 75% to 90%, has resulted in virtually universal acceptance that nicotine produces addiction.[8] Thus, nicotine's addictive effects are now undeniably foreseeable to manufacturers of cigarettes and smokeless tobacco products. Because it is also well known that nicotine addiction produces a physiological and psychological need for additional doses of nicotine, it is foreseeable that a large proportion of consumers will use tobacco to satisfy their addiction.

b. Other Pharmacological Effects. In addition to its addictive effects, nicotine produces a range of other significant pharmacological effects, which manufacturers of cigarettes and smokeless tobacco products can reasonably be expected to foresee. See p. 73 et seq. A large body of published evidence demonstrates that nicotine produces both stimulative and depressant effects on mood. See p. 75; see also p. 171. These psychoactive effects have been confirmed using electroencephalographic (EEG) analysis. Id. When smokers are in a stressful situation, smoking has a depressant effect on the EEG profile. When smokers are under conditions of low arousal, induced by mild sensory isolation, cigarette smoking has a stimulant effect. See pp. 75-76. In his 1988 report, the Surgeon General reviewed the epidemiological literature on the effects of smoking on mood. The report concluded:

> *The conclusion from this literature is that in the general population, persons perceive that smoking has functions that are relevant for mood regulation. Persons report that they smoke more in situations involving negative mood, and they perceive that smoking helps them to feel better in such situations . . . .*

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[8] This evidence distinguishes nicotine from caffeine-containing beverages and alcohol. If beverages containing caffeine are addictive, they are addictive in a very small percentage of users. Griffiths RR. Editorial: Caffeine dependence should be kept in proper perspective. *JAMA* 1994;272(13):1065-66. Beverages containing alcohol are addictive in fewer than 15% of users. Id. at p. 1066; Grant BF, Harford T, et al. Prevalence of DSM-II-R Alcohol Abuse and Dependence in the U.S., 1988. Alcohol Health and Research World Epidemiologic Bulletin No. 27, 1991;15(1):91.

See p. 118.

In addition, nicotine is widely believed to regulate weight gain in smokers. See p. 119. The 1988 Surgeon General's Report summarized the large number of clinical studies establishing an inverse relationship between cigarette smoking and body weight and animal studies demonstrating that nicotine plays an important role in the relationship between smoking and body weight. Id. Numerous studies show that smokers believe that smoking keeps weight down and that weight control is a significant motivation for continued smoking. Id.

This evidence plainly satisfies the objective standard for "intended use" set forth above. The widespread knowledge and acceptance of the very significant pharmacological effects of nicotine establish that any reasonable person would know that marketing nicotine-containing cigarettes and smokeless tobacco products will result in these effects and lead to addiction in millions of users.

This evidence is at least as strong as the evidence that the courts found to be sufficient to establish intended use in Jonas, Baby Rattles, and Focht, supra. As discussed above, in each of those cases, the defendant had a plausible argument that its product could be used for purposes that fell outside the jurisdiction of the relevant statute (e.g., baby rattles as party favors, firework components for use in legal fireworks). Nevertheless, the courts in each case found that the product fell within the jurisdiction of the applicable regulatory agency based on evidence that a foreseeable use of the product fell within the ambit of the statute. The pharmacologic effects and uses of nicotine-containing cigarettes and smokeless tobacco products are at least as foreseeable as the uses of the products at issue in Jonas, Baby Rattles,

and Focht.

2. Consumers Use Tobacco Products to Obtain the Pharmacological Effects of Nicotine and to Satisfy Their Addiction to Nicotine.

As previously explained, the intent that a product be used as a drug may also be shown by evidence, alone or in combination with other evidence, that consumers use it for pharmacological purposes. Here, the evidence establishes that consumers use tobacco for three pharmacological purposes: to satisfy a nicotine addiction; to receive the accompanying psychoactive effects, such as relaxation and stimulation; and to control weight. Moreover, the evidence shows that consumers use cigarettes nearly exclusively for pharmacological purposes. As discussed above, under the most widely used definitions, major recent studies show that 75% to 90% of frequent cigarette users are addicted to cigarettes. See p. 26. Studies also reveal that a large proportion of consumers use tobacco for other pharmacological effects, including relaxation, reduction of negative feelings, and for controlling weight. See p. 118 et seq. Under ASH, 655 F.2d at 240, and NNFA, 557 F.2d at 336, the high percentage of smokers who use cigarettes for their pharmacological effects, particularly to satisfy an addiction, one of the most significant drug effects on the body possible, is sufficient by itself to classify cigarettes and smokeless tobacco products as drug delivery systems within the meaning of the Act.

Even if the evidence of consumer use of tobacco products to satisfy addiction and to obtain other pharmacological effects were not alone sufficient to establish the intended use of cigarettes and smokeless tobacco products, the evidence of consumer use, in combination with the other evidence presented here, provides compelling support for the determination

that these products are intended to be used for pharmacological purposes. Indeed, the nature of consumer use of these products underscores nicotine's classification as a drug. Because nicotine is an addictive product that the vast majority of consumers use on a daily basis for a period of years, if not a lifetime, to satisfy an addiction, nicotine unquestionably functions as a pharmacological product at the consumer level. See also LEGAL ANALYSIS § II.B.3, infra (tobacco manufacturers recognize and acknowledge that consumers use their products to obtain the pharmacological effects of nicotine).

In summary, consumers' use of cigarettes and smokeless tobacco products for nicotine's pharmacological effects, viewed in combination with the other evidence presented here, supplies more than sufficient evidence to show that nicotine-containing cigarette and smokeless tobacco products are drug delivery systems within the meaning of the Act.

3. Tobacco Manufacturers Know That Nicotine Has Pharmacological Effects and That Consumers Use Tobacco for Those Effects, and Have Acted to Facilitate That Use.

Nicotine's psychoactive and addictive effects on tobacco users are plainly foreseeable to tobacco manufacturers, not only because they are widely known and published in scientific, governmental, and lay publications, but because for over 30 years the manufacturers themselves have engaged in intensive research on nicotine's psychoactive and addictive effects. In addition, tobacco industry documents reveal numerous statements by both industry researchers and executives in which they express their own views that nicotine in tobacco products acts as a psychoactive and addictive drug. Tobacco manufacturers' own research also demonstrates that consumers use cigarettes to obtain the pharmacological effects of

nicotine. Finally, tobacco manufacturers have conducted numerous studies to identify the dose of nicotine that will elicit the psychoactive effects sought by tobacco users, and manipulate the amount of nicotine delivered by tobacco products.

a. Tobacco Manufacturers' Studies and Statements Demonstrate Knowledge That Nicotine in Tobacco Is Addictive and Has Psychoactive Effects.

(i.) Addiction. Over the last 35 years, the tobacco industry has conducted many studies that collectively demonstrate that nicotine has the properties of an addictive drug. As described in FINDINGS § I.A.2., infra, substances are shown to have addictive properties by studies of the substance in animals, studies of human reactions to the substance, and studies of effects on the brain caused by the substance.

Two kinds of animal studies are highly predictive of a substance's addictive properties: self-administration studies and drug discrimination studies. See pp. 94-97. A substance is considered a "positive reinforcer" that is highly likely to be addictive in humans if studies show that animals self-administer the substance. Id. In drug discrimination studies, potentially addictive substances are identified by comparing the effects of one substance to those of other psychoactive substances. Id.

As noted above, under the major definitions of addiction, a substance is recognized as producing addiction (dependence) on the basis of studies on human responses to the substance if:

- the substance is psychoactive; i.e., mood altering;
- patterns of use are regular and compulsive, despite attempts to quit and harmful consequences;

- it causes physical dependence characterized by a withdrawal syndrome; and/or
- tolerance develops, causing diminished effects after repeated use and increased intake.

See p. 79 et seq.

The tobacco industry has conducted or funded studies in both animals and humans showing that nicotine bears each of these hallmark properties of an addictive substance. Industry-conducted and sponsored research has shown that animals self-administer nicotine and that animals experience nicotine's psychoactive effects. See p. 180 et seq. Industry research also demonstrates that the human response to nicotine in tobacco meets generally accepted definitions of addiction. Tobacco industry research demonstrates that nicotine has psychoactive effects, see p. 171, that most tobacco consumers continue daily use of tobacco, despite serious attempts to quit and despite concerns about the adverse health consequences of tobacco use, see p. 206 et seq., and that abstinence from tobacco use produces a withdrawal syndrome. See pp. 146, 182. Tolerance to the pharmacological effects of nicotine has also been closely studied by the tobacco industry and demonstrated in both animals and humans. See p. 181. Finally, tobacco industry studies have shown that nicotine acts on the mesolimbic system in the brain and triggers the release of the chemical dopamine. See p. 170. It is believed that dopamine release is the mechanism by which several of the most significant drugs of abuse, including cocaine and amphetamines, exert their addictive effects. See p. 74. Thus, the tobacco industry's own research demonstrates that nicotine has all the properties of an addictive drug.

Numerous tobacco company documents contain statements by company researchers and executives acknowledging that nicotine is, in fact, addictive. See p. 143 et seq. More

than 30 years ago, a report was completed for British-American Tobacco Co. (BATCO)[9] that specifically addressed the mechanism of nicotine addiction in smokers. See p. 143. The researchers concluded that chronic intake of nicotine, such as that which occurs in regular smokers, creates a need for ever-increasing levels of nicotine to maintain the desired action: "[u]nlike other dopings, such as morphine, the rate of increasing demand for greater dose levels is relatively slow for nicotine." Id. The report continues:

> *A body left in this unbalanced state craves for renewed drug intake in order to restore the physiological equilibrium. This unconscious desire explains the addiction of the individual to nicotine.*

See p. 144.

Dr. Sidney J. Green, the director of research for BATCO for 20 years and a member of the company's board of directors, repeatedly acknowledged that nicotine is addictive. See p. 150. Dr. William L. Dunn, a senior scientist at Philip Morris similarly made repeated statements that reflect the view that nicotine has the properties of an addictive substance. See pp. 152-154.

On the basis of research that had been sponsored by the industry in the early 1960's, the general counsel to Brown and Williamson reached the conclusion that "[w]e are, then, in the business of selling nicotine, an addictive drug . . . ." See p. 150. There have been more recent acknowledgements by the industry that nicotine is addictive, although industry representatives have been much more reticent in the statements they have made about nicotine's addictive properties since the 1970's, when product liability concerns began to

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[9] BATCO and Brown and Williamson Tobacco Corp, both part of the multi-national BAT Industries, PLC, shared both the funding and the results of their nicotine-related research. *See* Appendix 2.

mount. Throughout the 1970's and 1980's, industry-funded researchers have repeatedly stated that nicotine produces addiction, dependence, and withdrawal. See p. 145 et seq., 179-80. Moreover, in 1994, a recently retired CEO of a major tobacco company openly stated that tobacco is addictive and that its addictive properties are why people smoke. In an interview for an article in the Wall Street Journal, the former chief executive of RJR Nabisco, F. Ross Johnson, was asked about nicotine in cigarettes, and he responded, "Of course it's addictive. That's why you smoke . . ." See p. 155.

(ii.) Psychoactive Effects. The tobacco industry has conducted and funded, both as individual companies and through the jointly-operated Council for Tobacco Research (CTR),[10] hundreds of studies evaluating nicotine's pharmacological effects on the brain, including nicotine's specific physiological effects on brain structure and chemistry; its effects on mood, performance, and cognition; and its capacity to produce the characteristic features of addiction. See FINDINGS § II.B., infra, at p. 160 et seq.

Internal company documents reveal that the industry conducted and funded this research effort on the effects of nicotine on the brain because the tobacco manufacturers strongly suspected, as long as 30 years ago, that nicotine's drug effects were the basis for the world tobacco market. See p. 161. For example, in 1963, researchers for one company urged further study of nicotine because "nicotine is the key factor in controlling, through the central nervous system, a number of beneficial effects of tobacco smoke." See p. 161 (emphasis added). In the early 1960's, a prominent industry scientist, Sir Charles Ellis, the scientific

[10] The Council for Tobacco Research is an industry trade association that represents almost all of the major tobacco producers in the United States. *See* note 176, *infra.*

advisor to the board of directors of BATCO, explained that industry-sponsored research was underway "to elucidate the effects of nicotine as a beneficent alkaloid drug," and stated "we are in a nicotine rather than a tobacco industry." See p. 161. Indeed, the industry as a whole was sponsoring substantial research on nicotine pharmacology because of the shared belief that the drug effects of nicotine were central to tobacco use. See pp. 140-42.

Over the next 30 years, the tobacco industry conducted numerous studies on the drug effects of nicotine that appear similar to the studies conducted by pharmaceutical companies. Before marketing prescription drugs, a pharmaceutical company studies the pharmacokinetics of the drug (how it is absorbed into the body, metabolized, and excreted), the pharmacodynamics of the drug (what specific effects the drug has on the body's chemistry and metabolism as it makes its way through the body), and the clinical effects of the drug (whether the drug is effective in producing the desired therapeutic or physiological effect). The tobacco industry has conducted and funded hundreds of studies on nicotine's pharmacokinetics, pharmacodynamics, and clinical effects. See p. 160 et seq. As a result, the tobacco industry appears to have an understanding of the pharmacological effects produced by the nicotine in tobacco analogous to that which a pharmaceutical company has in marketing a new drug.

For example, the tobacco industry has developed sophisticated techniques for determining, quantitatively and qualitatively, the presence of nicotine and its metabolites in blood, urine, and tissue. See p. 174. Studies sponsored by tobacco companies using these techniques have shown that nicotine from tobacco is absorbed into the bloodstream and delivered to the brain, see p. 176, and that, once delivered to the brain, nicotine acts on the

receptors in the brain that produce a range of significant effects on brain chemistry and metabolism. See pp. 164, 169.

The tobacco industry has also sponsored many studies on the ultimate psychoactive effects produced by nicotine. Studies sponsored by the tobacco industry have repeatedly demonstrated that nicotine induces moods changes, which, under different conditions, provide both stimulant and depressant (relaxant) effects. See pp. 171-72. Moreover, tobacco industry studies have shown that nicotine's effects on mood are correlated to EEG changes (a measurement of electrical activity in the brain that is indicative of pharmacological activity on the central nervous system). Id. The tobacco industry has also conducted many studies that attempt to show that nicotine improves performance efficiency. See p. 173.[11]

Internal tobacco company documents reveal that all of this research has convinced company researchers and executives that nicotine in tobacco functions as a drug with powerful psychoactive effects. For example, in 1962, even before much of this research had been completed, Sir Charles Ellis, of BATCO, expressed his view that nicotine in tobacco functions as a drug much like stimulants and tranquilizers:

> *It is my conviction that nicotine is a very remarkable beneficent drug that both helps the body to resist external stress and also can as a result show a pronounced tranquilising effect. You are all aware of the very great increase in the use of artificial controls, stimulants, tranquilisers, sleeping pills, and it is a fact that under modern conditions of life people find that they cannot depend just on their subconscious reactions to meet the various environmental strains with which they are confronted: they must have drugs available which they can take when they feel the need. Nicotine is not only a very fine drug, but the techniques of administration by smoking has considerable psychological advantages and a built-in control against excessive absorption.*

[11] In fact, these studies show only that tobacco users perform better on some cognitive tasks when they are given nicotine than when deprived of cigarettes or nicotine. The studies do not show that tobacco users perform better than non-tobacco users. *See* FINDINGS § II.A.2., *infra*.

See p. 139 (emphasis added). In the decades that followed this statement, BATCO and Brown and Williamson held many research conferences, some of which were devoted entirely to discussing nicotine's pharmacological effects. The records of these conferences demonstrate that, at almost every conference, tobacco company officials from around the world discussed the results of research on nicotine pharmacology and reached agreement that nicotine had been shown to have pharmacological effects on tobacco users. See p. 125 et seq.

Researchers and executives from the other major tobacco companies and associated with CTR have also made statements revealing their knowledge that nicotine is a psychoactive drug. For example, the authors of a research paper funded by CTR reporting on the "beneficial" pharmacological effects of nicotine in cigarettes said that "[n]icotine is recognized as the primary psychoactive compound in cigarette smoke." See p. 131.

Researchers at RJR have published studies in which they freely acknowledge the pharmacological effects of nicotine in tobacco. In one study, they concluded that "the beneficial effects of smoking on cognitive performance . . . are a function of nicotine absorbed from cigarette smoke upon inhalation." Another published RJR study discusses the "nicotine paradox": the effects of smoking that appear to be stimulating (e.g., increased heart rate) and to increase mental alertness are inconsistent with nicotine's calming and stress-reduction effects. See p. 129. As discussed in the following subsection, documents containing statements from Philip Morris officials and officials at U.S. Tobacco, the largest smokeless tobacco manufacturer, show that executives at these companies also believe that nicotine in tobacco is a psychoactive drug.

b. Tobacco Manufacturers Know That Consumers Use Tobacco Products for the Pharmacological Effects of Nicotine.

Industry documents show that tobacco manufacturers have thoroughly researched consumer use of tobacco products and understand that consumers use tobacco to obtain the pharmacological effects of nicotine. In fact, tobacco manufacturers believe that consumers will not accept cigarettes that contain insufficient levels of nicotine to produce pharmacological effects.

BATCO reports, research conference proceedings, and other internal documents from BATCO contain repeated assertions that consumers use tobacco largely to obtain nicotine's pharmacological effects. See p. 125 et seq. A BATCO Group R&D Smoking Behaviour-Marketing Conference held in 1984, which focused almost entirely on the role of nicotine pharmacology in smoking, included a presentation in which the following statement was made:

> *Smoking is then seen as a personal tool used by the smoker to refine his behaviour and reactions to the world at large.*
>
> . . . .
>
> *It is apparent that nicotine largely underpins these contributions through its role as a generator of central physiological arousal effects which express themselves as changes in human performance and psychological well-being.*

See pp. 126-27 (emphasis added). At a 1976 BATCO Smoking Behavior Conference, the conferees were so convinced that obtaining a dose of nicotine was the reason people smoke that they thought that other, non-pharmacological reasons for smoking might emerge only after the smoker had achieved a "maximum nicotine level" and had satisfied his desire for nicotine. See p. 194. Many other industry statements described in FINDINGS, § II.A.1 and C., infra, also show that the tobacco industry knows that the pharmacological effects of

nicotine are the primary reason consumers use cigarettes and smokeless tobacco products.

Industry documents also reveal that tobacco manufacturers appreciate that consumers will not accept individual tobacco products unless they provide a pharmacologically satisfying dose of nicotine. Dr. Helmut Wakeham of Philip Morris stated in 1961 that the pleasures of smoking derive at least in part from nicotine's pharmacological effects and that "nicotine is believed essential to cigarette acceptability." See p. 134. This view was later adopted and enlarged by William Dunn, Jr., another high-ranking Philip Morris official. In summarizing a 1972 conference sponsored by CTR, Dunn reported that "[t]he primary incentive to cigarette smoking is the immediate salutary effect of inhaled smoke upon body function." See p. 134. Dunn continued:

> *The majority of the conferees would go even further and accept the proposition that nicotine is the active constituent of cigarette smoke. Without nicotine, the argument goes, there would be no smoking. Some strong evidence can be marshalled to support this argument:*
>
> *1) No one has ever become a cigarette smoker by smoking cigarettes without nicotine.*
>
> *2) Most of the physiological responses to inhaled smoke have been shown to be nicotine-related.*
>
> *3) Despite many low nicotine brand entries in the market place, none of them have captured a substantial segment of the market . . . .*

See p. 135 (emphasis added).

Tobacco industry documents on "satisfaction" also demonstrate industry knowledge that delivery of a pharmacologically active dose of nicotine is essential to consumer acceptance of tobacco products, see FINDINGS § II.C.1., infra, and that "satisfaction" is a tobacco industry euphemism for the pharmacological response to nicotine that smokers seek

to obtain from smoking. See p. 185. For example, a BATCO scientist, in a 1969 presentation describing the research activities of BATCO Group Research & Development, stated that:

> *Nicotine has well documented pharmacological action. It is claimed to have a dual effect, acting both as a stimulant and a tranquilliser. It is believed to be responsible for the "satisfaction" of smoking, using this term in the physiological rather than the psychological sense.*

See p. 186. An RJR Marketing Summary Report from 1983 similarly concludes that the primary reason people smoke "is probably the physiological satisfaction provided by the nicotine level of the product." See p. 186 (emphasis added). These and other industry statements set forth in FINDINGS § II.C.1., infra, further demonstrate the tobacco manufacturers' awareness that consumer "satisfaction" from tobacco products depends upon delivery of pharmacologically satisfying amounts of nicotine.

The industry's study of "compensation" behavior by smokers provides further telling evidence of the industry's awareness that consumers use tobacco to obtain a carefully titrated dose of nicotine. See FINDINGS § II.C.3., infra, p.198 et seq. "Compensation" refers to the behavior of smokers when given cigarettes that provide a lower nicotine yield than their regular brands (as measured by a smoking machine). When using lower-dose products, smokers often smoke more cigarettes or smoke the cigarette more intensely, for example, by taking larger or more puffs. Tobacco company documents reveal that the industry recognizes both that smokers compensate and that the purpose of compensation behavior is to allow smokers to achieve a dose of nicotine that satisfies their physiological need for nicotine. Id.

The tobacco industry has conducted studies on compensation that show that each smoker tends to obtain close to the same dose of nicotine from each cigarette, despite differences in the yield as measured by a smoking machine. See pp. 202-04. In other words,

industry studies show that tobacco users seek a specific dose of nicotine from tobacco and adjust their smoking behavior to obtain their customary dose of nicotine from cigarettes with different yields. For example, in 1974, BATCO researchers reported on a study that found that "the smoker adjusts his pattern to deliver his own nicotine requirements (about 0.8 mg per cigarette)." See p. 202. Thus, the tobacco industry's studies demonstrate that smokers use the cigarette as a nicotine delivery system and vary their smoking behavior to obtain specific doses of nicotine.

Tobacco company documents demonstrate not only the tobacco industry's awareness of the fundamental importance of nicotine's effects on the brain, but their knowledge that these effects motivate almost all smoking. A 1977 BATCO report entitled "Some 'Benefits' of Smoking" contained the following statement:

> *Some insights into the likely benefits of smoking follow from a consideration of the properties of nicotine, which is considered to be the reinforcing factor in the smoking habit of at least 80% of smokers* . . . .

See p. 132 (emphasis added). High-ranking officials agreed with this assessment. Dr. S.J. Green of BATCO, the Director of Research and member of the Board of Directors of BATCO, wrote in 1972 that the "[t]he tobacco smoking habit is reinforced or dependent upon the psycho-pharmacological effects mainly of nicotine." See p. 140.

The smokeless tobacco industry also recognizes that almost all consumers use tobacco products to obtain the pharmacological effects of nicotine. The senior vice-president for marketing of U.S. Tobacco wrote in a 1981 letter on new product development:

> *Flavorwise we should try for innovation, taste and strength, nicotine should be medium . . . Virtually all tobacco usage is based upon nicotine, "the kick," satisfaction.*

See pp. 186-87 (emphasis added).

The importance of nicotine delivery to consumer acceptance of tobacco products is so well-recognized by the tobacco industry that tobacco company officials themselves consider tobacco products to be nicotine delivery systems, i.e., vehicles for administering doses of nicotine. At the 1984 BATCO Smoking Behaviour-Marketing Conference, which focused heavily on the central role of nicotine's pharmacological effects in tobacco use, one of the presentations included a slide that read "in its simplest sense puffing behaviour is the means of providing nicotine dose [sic] in a metered fashion." See p. 159.

Tobacco company documents demonstrate that high-ranking tobacco company officials share the view that tobacco is a nicotine delivery system. See FINDINGS § II.A.3., infra, at p. 156 et seq. Dr. Green repeatedly asserted that tobacco is simply a vehicle for delivering nicotine. See p. 157. RJR executive Claude Teague, Jr. wrote:

> *In a sense, the tobacco industry may be thought of as being a specialized, highly ritualized, and stylized segment of the pharmaceutical industry. Tobacco products uniquely contain and deliver nicotine, a potent drug with a variety of physiological effects . . . . If nicotine is the sine qua non of tobacco products, and tobacco products are recognized as being attractive dosage forms of nicotine, then it is logical to design our products - and where possible our advertising - around nicotine delivery . . .*

See pp. 156-57.

In summarizing a 1972 conference sponsored by the CTR, William Dunn, of Philip Morris, characterized the cigarette as a nicotine delivery system in the following language:

> *Think of the cigarette pack as a storage container for a day's supply of nicotine . . . Think of the cigarette as a dispenser for a dose unit of nicotine . . . Think of a puff of smoke as the vehicle of nicotine . . . Smoke is beyond question the most optimized vehicle of nicotine and the cigarette the most optimized dispenser of smoke.*

See p. 156.

Thus, tobacco company researchers and executives have not only acknowledged that nicotine's drug effects are central to the use of tobacco, but have also stated their intention that tobacco products be used as delivery systems to administer doses of nicotine.

c. Tobacco Manufacturers Have Acted to Facilitate and Sustain the Consumer Use of Tobacco Products for Their Pharmacological Effects.

The amount of nicotine that reaches the bloodstream of the smoker is determined by the nicotine content of the leaf, the chemical additives used during processing of the tobacco, and the design of the cigarette or smokeless tobacco product. FDA's investigation has revealed that tobacco manufacturers have conducted numerous studies to identify the dose of nicotine that will elicit the pharmacological effects sought by the products' users. See FINDINGS § II.C.2, infra, at p. 188 et seq. Furthermore, the investigation has shown that cigarette and smokeless tobacco companies manufacture their products to specifications that ensure that the final product will contain precise levels of nicotine. See FINDINGS § II.E., infra at p. 232 et seq. This evidence also demonstrates that tobacco manufacturers know and intend that the nicotine in their products have pharmacological effects on consumers.

(i.) Product Development Research. The tobacco industry is not only keenly aware that consumers use tobacco for nicotine's pharmacological effects, but has conducted product development research designed to ensure that tobacco products deliver a sufficient dose of nicotine to provide a pharmacological response that satisfies the users' need for nicotine. See FINDINGS §§ II.C.1. and 2., infra. The industry has developed sophisticated technology to

determine the amount of nicotine absorbed by tobacco users. See p. 191. Using this technology, tobacco manufacturers have shown that tobacco users have a "daily nicotine requirement." See p. 192. Industry research and statements also show that the industry has devoted substantial resources to determine what dose of nicotine must be delivered by each cigarette and has attempted to establish the "minimum dose of [ ] nicotine that can provide pharmacological satisfaction for the smoker." See p. 190. The tobacco industry has also focused a significant portion of its product development research on methods of ensuring that nicotine is delivered at levels that do not fall below a pharmacologically satisfying dose.

In 1972, William Dunn, Jr., of Philip Morris expressed the widely held industry view that there is a minimum level of nicotine that must be delivered in tobacco products to provide pharmacological effects, and that below that level there would be few, if any, tobacco sales:

> *[C]ritics of the industry would do well to reflect upon the indifference of the consumer to the industry's efforts to sell low-delivery brands. 94% of the cigarettes sold in the U.S. deliver more than 1 mg of nicotine. 98.5% deliver more than 0.9 mg. The physiological response to nicotine can be readily elicited by cigarettes delivering in the range of 1 mg of nicotine.*

See p. 189 (emphasis added).

The industry has conducted many studies designed to establish the daily dose of nicotine obtained by tobacco users and the amount of nicotine that individual tobacco products must deliver to the consumer to provide that dose. See FINDINGS § II.C.1. and 2., infra. For example, Project Wheat was a multi-part study intended to aid BATCO in developing cigarettes with increased consumer acceptance and, specifically, to establish smokers' preferred nicotine level in tobacco products. See pp. 183-84. Reports of the study

make clear that the research was designed to identify the dose of nicotine that would produce desired physiological responses, rather than to identify the correct level of nicotine for taste or flavor. One report states:

> *In considering which product features are important in terms of consumer acceptance, the nicotine delivery is one of the more obvious candidates. Others include the taste and flavour characteristics of the smoke, physical features such as draw resistance and rate of burn, and the general uniformity of the product, to name but a few. The importance of nicotine hardly needs to be stressed, as it is so widely recognized.*

See p. 184 (emphasis added). The researchers offered cigarettes containing different levels of nicotine to smokers and studied their responses. The study report concludes that there was an optimum nicotine delivery for smokers. The study also found that there was a minimum level of nicotine necessary to satisfy all smokers and that cigarettes that provided nicotine below that level were unacceptable. See p. 189. Project Wheat and similar industry studies and statements, FINDINGS § II.C.1. and 2., infra, reveal that tobacco manufacturers know that tobacco products must deliver a pharmacologically active level of nicotine to maintain consumer acceptance, and that manufacturers have acted to identify that level.

Other tobacco industry research reveals that the tobacco industry has taken action to ensure that tobacco products in fact deliver pharmacologically satisfying doses of nicotine. See FINDINGS § II.D., infra, at p. 213 et seq. As described above, the industry is well aware that tobacco products must provide a certain level of nicotine to elicit the pharmacological effects sought by consumers and that consumers will not continue to purchase tobacco products that fall below that threshold. As a result, the industry has focused substantial attention on methods of manipulating nicotine delivery in marketed products. In particular, the industry has devoted considerable research to reducing tar while maintaining a level of

nicotine delivery that would satisfy consumers' desire for the pharmacological effects of nicotine. See FINDINGS § II.D.2., infra at p. 222 et seq. As stated in one industry patent:

> *Maintaining the nicotine content at a sufficiently high level to provide the desired physiological activity, taste, and odor . . . can thus be seen to be a significant problem in the tobacco art. The addition of nicotine to tobacco in such a way that it remains inert and stable in the product and yet is released in a controlled amount into the smoke aerosol when the tobacco is pyrolyzed, is a result which is greatly desirable.*

See p. 213-14 (emphasis added).

As early as 1965, a Brown and Williamson official reported to other Brown and Williamson executives that BATCO research was focused on "the smoking and health problem." The goal was "to find ways of obtaining maximum nicotine for minimum tar." See p. 225. Approaches being used include: (a) chemical treatment of filters; (b) nicotine fortification of cigarette paper; (c) addition of nicotine containing powders to tobacco; (d) alteration of blends." Id.

An abundance of industry studies and patents show that in the decades since 1965, the tobacco industry has invested substantial resources to develop methods and technologies, the declared purpose of which is to facilitate the design of cigarettes in which the tar has been lowered but the amount of nicotine delivered has been maintained or increased. See FINDINGS § II.D.2., infra. These methods and technologies include: increasing the nicotine content of tobaccos by, for example, adding commercial nicotine to the tobacco or other parts of the cigarette, see pp. 214-16; transferring nicotine from one tobacco to another or by adding tobacco extracts, see p. 217; adding chemicals to tobacco and filters to increase delivery of nicotine, without altering nicotine content, see p. 228; and altering the "puff-by-puff" delivery of nicotine, see p. 227.

Tobacco manufacturers have also attempted to help smokers compensate for lower nicotine yields, that is to obtain more nicotine from a cigarette than its machine-tested yield, by designing cigarettes with "elasticity." See p. 229 et seq. ("Elasticity" refers to the ability of a cigarette, whatever its machine-measured nicotine yield, to deliver enough smoke to permit a smoker to obtain the amount of nicotine he needs, for example, through more or longer puffs, or by covering ventilation holes.) BATCO researchers described corporate policy on compensation and elasticity at a 1984 conference:

> *Compensation by modifying smoking regime [increasing or decreasing puff volume, duration, puff frequency, amount inhaled] is a topic which is being explored at GR & DC and this includes designing products which aid smoker compensation.*
>
> *The marketing policy concerning this type of product is not clear but it is believed it will depend largely on the degree of elasticity in the design and how overtly this elasticity is achieved. The consensus is that small improvements in elasticity which are less obvious, visually or otherwise is likely to be an acceptable route.*

See p. 230 (emphasis added). BATCO documents reflect numerous examples of research on different methods to improve elasticity. See p. 230.

In summary, the tobacco industry's product development research confirms that: tobacco manufacturers know that consumers use tobacco for its pharmacological effects; have acted to establish the dose that consumers require to obtain pharmacological satisfaction from tobacco products; and have worked to develop technology that will ensure that marketed products deliver a pharmacologically satisfying dose of nicotine.

(ii.) Control Over Nicotine Levels. Tobacco manufacturers also deliberately control the level of nicotine in cigarettes by monitoring and adjusting nicotine levels at each stage of the manufacturing process. The ultimate objective of these efforts is to ensure that the finished cigarette delivers the desired level of nicotine.[12]

Perhaps the best example of manufacturers' control of nicotine levels is the effort that the companies make to ensure that low-tar cigarettes deliver an adequate amount of nicotine. As described in the preceding subsection, tobacco industry research activities have focused on developing technologies for maintaining and increasing nicotine levels as tar is reduced. FDA's investigation has also shown that tobacco manufacturers actually use a number of techniques to ensure that nicotine levels in marketed products do not fall below a certain level, such as incorporating high nicotine tobaccos to ensure "adequate" levels of nicotine and using chemical additives to enhance nicotine delivery.

Tobacco manufacturers have a sophisticated understanding of the nicotine levels in various types of tobacco and in the various parts of the tobacco plant. By monitoring nicotine levels in the tobacco they purchase and by blending the tobaccos in accordance with their nicotine levels, tobacco companies are able to manufacture tobacco products with nicotine levels that vary only minimally within cigarette packs and from pack to pack. See p. 271.

Officials at R.J. Reynolds and Brown and Williamson have confirmed the importance

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[12] A number of techniques of cigarette production and manufacture can be used to lower nicotine levels. Probably the most significant technique is the design of low-tar cigarettes which lower nicotine levels when they lower tar levels. The filters that are used in 95% of cigarettes sold in the United States remove a certain amount of nicotine. The techniques described in FINDINGS § II.E., *infra*, are used by the tobacco industry to offset these reductions in nicotine levels and ensure that each cigarette delivers an amount of nicotine necessary to ensure consumer "satisfaction," i.e., to provide an adequate dose of nicotine to produce desired pharmacological effects.

of nicotine levels in leaf growing and purchasing. See p. 243. At least one company has actually developed a high-nicotine tobacco to use in manufacturing low-tar cigarettes. Brown and Williamson used a combination of conventional and advanced genetic breeding techniques to develop a high-nicotine, flue-cured tobacco plant, named "Y-1," that has approximately twice the nicotine level of American-grown flue-cured tobacco. Brown and Williamson used Y-1 tobacco in its cigarettes. See p. 239 et seq.

Once purchased, tobacco leaves are blended to attain target levels of nicotine. In fact, nicotine content is maintained at levels that would represent a high degree of control for a conventional drug manufactured from synthetic, homogeneous materials. See pp. 246-47. This level of control is remarkable for a product such as cigarettes, which are made from biological materials with a highly variable content.

Where design features aimed at reducing tar levels have also lowered nicotine levels, the manufacturer can use tobacco leaves with higher nicotine content to increase the nicotine level. For example, filters that are designed to reduce tar can also reduce nicotine. Yet, the industry is known to use proportionally greater amounts of higher nicotine-containing tobaccos in the tobacco blends of the lowest-tar varieties of cigarettes to maintain a higher nicotine level in those products. See p. 247. For example, "Y-1," Brown and Williamson's high-nicotine tobacco, was developed as a "blending tool" to permit the company to reduce tar and yet maintain nicotine delivery in its low-tar cigarettes. See p. 240.

Chemical additives are also used to enhance nicotine delivery. A major American tobacco company's 1991 handbook on leaf blending and product development identified ammonia as being effective to increase the amount of nicotine delivered to the smoker.

According to the handbook, ammonia in cigarette smoke "can liberate free nicotine from the blend, which is associated with increases in impact and 'satisfaction' reported by smokers." See p. 249. American tobacco companies often use ammonia in reconstituted tobacco; when cigarettes containing this type of tobacco are burned, the reconstituted tobacco serves as a source of ammonia in the cigarette smoke. See p. 250.

Tobacco companies also use a number of other chemicals to optimize nicotine delivery. Nicotine has a naturally harsh taste. To maintain sufficiently high levels of nicotine in tobacco products, manufacturers moderate nicotine's harshness by adding flavors such as sugar, licorice, cocoa, menthol, and other alcohol-based aromic substances to tobacco. According to one industry expert, the major contribution of the tobacco flavor specialist is to "help provide a rich, clean, full-bodied tobacco flavor, to keep to a minimum hotness and irritation in the mouth, and to ensure high satisfaction from an adequate level of nicotine per puff[,] requirements that guarantee the consumer a pleasurable smoke." See p. 251. In addition, glycerine/glycol in aerosol formulation is used to enhance "smoothness," ensuring that smoke will be inhaled into the lungs, thereby facilitating rapid and complete absorption of nicotine. See p. 253.

To a remarkable degree, the cigarette industry has accomplished the task of delivering sufficiently high levels of nicotine in low-tar products. A 1983 study showed that cigarettes advertised as having a low-nicotine yield contain as much nicotine as high-yield cigarettes. See p. 262. Moreover, all marketed cigarettes deliver sufficient nicotine to produce pharmacological effects on smokers. See p. 108 et seq. These findings are consistent with FDA's findings that the industry employs a number of methods to boost nicotine delivery to

compensate for nicotine losses from the application of tar-reducing designed modifications. Without the use of such methods, the techniques used to reduce tar should result in corresponding nicotine reductions. Instead, studies by FDA and others have demonstrated that the nicotine yield of cigarettes, as defined by the Federal Trade Commission (FTC) smoking machine tests, correlates inversely with nicotine concentrations in the tobacco, i.e., that some of the lowest-tar cigarettes have the highest concentrations of nicotine. See p. 262 FDA's analysis of FTC data also reveals an apparent increase in the sales-weighted FTC nicotine delivery ratings since 1982 (the earliest year for which the computer database is available), i.e., an overall increase in nicotine delivery from U.S. cigarettes. See p. 266.

Tobacco manufacturers' actions to manipulate nicotine deliveries from marketed cigarettes further demonstrate that nicotine is the central component of tobacco products, and that tobacco manufacturers have taken deliberate steps to maintain the level of nicotine that smokers receive.

(iii.) Alternative Product Research. Tobacco manufacturers have researched and developed alternatives to conventional tobacco products and to nicotine, largely in response to concerns about the health effects of conventional tobacco products. See FINDINGS § II.F., infra, p. 289 et seq. Industry documents explaining the nature and purpose of these alternative products provide confirmation that tobacco manufacturers: 1) understand that nicotine's pharmacological effects on the brain are essential to the successful marketing of tobacco products, and 2) have taken actions to ensure that alternative tobacco products will continue to provide these pharmacological effects.

Internal documents from both Philip Morris, Inc., and Brown and Williamson show

that these companies have had substantial research programs to identify "nicotine analogues," chemicals that are closely related to nicotine. See FINDINGS § II.F.1., infra. Company documents reveal that both Philip Morris and Brown and Williamson were seeking analogues that would produce effects on the central nervous system similar to nicotine, that could be substituted for nicotine if nicotine-containing tobacco became regulated or unattractive to consumers, and that could be added to currently marketed products to enhance the effects of nicotine. See p. 289. These programs were also designed to identify substances that shared nicotine's "desired" effects on the central nervous system, without producing its undesirable effects on the cardiovascular system. See p. 290.

The industry's nicotine analogue research programs were expressly based on the companies' view that "[s]hould nicotine become less attractive to smokers, the future of the tobacco industry would become less secure .... A commercial threat would arise if either an alternative [nicotine] product became acceptable or the effect of nicotine was changed [by an antagonist to nicotine]." See p. 292. In 1968, BATCO researchers, acknowledging the critical importance of nicotine in tobacco, recommended that the industry search for nicotine substitutes with the "desired" pharmacological effects on the brain:

> *In view of its pre-eminent importance, the pharmacology of nicotine should continue to be kept under review and attention paid to the possible discovery of other substances possessing the desired features of brain stimulation and stress-relief without direct effects on the circulatory system. The possibility that nicotine and other substances together may exert effects larger than either separately (synergism) should be studied and if necessary the attention of Marketing Departments should be drawn to these possibilities.*

See p. 290 (emphasis added). Various BATCO documents show that the company had an extensive program to identify nicotine analogues. See FINDINGS § II.F.1., infra.

Internal documents from Philip Morris' nicotine analogue program reveal that this company also sought nicotine analogues with pharmacological effects on the central nervous system, including effects associated with addiction. See p. 293 et seq. Philip Morris documents state explicitly that the purpose of the research on nicotine analogues was to find nicotine substitutes that were behaviorally active and had the same "reinforcing properties" in animals as nicotine. In an internal report on Philip Morris research, a section entitled "Nicotine Analogues" includes the following "research objectives":

1. *Determine if behaviorally active nicotine analogues can be directly substituted for nicotine in rats for which nicotine is functioning as an intravenously delivered positive reinforcer.*

2. *Establish nicotine analogues as an intravenously delivered positive reinforcer.*

3. *Compare the potencies of nicotine analogues to nicotine in producing positive reinforcing effects.*

See p. 296. As described in FINDINGS § I.B., infra, it is well established that the ability of a substance to act as a "positive reinforcer" is one of the hallmarks of an addictive substance. Philip Morris documents show that the company also tested nicotine analogues using "prostration" studies and "drug discrimination" studies. See p. 295. These studies provide evidence about whether a substance acts on the brain in the same manner as nicotine and has properties of an addictive substance. See FINDINGS § I.B., infra.

Philip Morris has also conducted pharmacological and behavioral research on another constituent of cigarette smoke, acetaldehyde, that was believed to have reinforcing effects. See FINDINGS § II.F.2, infra. This research was intended to find a combined dose of acetaldehyde and nicotine in cigarettes that would produce "maximal reinforcing effects."

See p. 298. The reinforcing efficacy of a substance is a measure of its ability to cause addiction in users. Id. In undertaking research on how to maximize the reinforcing effects of cigarettes, Philip Morris demonstrated its understanding of the addictive nature of cigarettes and its intention to produce, and even increase, these effects in tobacco users.

These company documents show that tobacco manufacturers have sought substitutes for nicotine that had psychoactive effects and other recognized characteristics of an addictive substance. At least one company conducted research on how to increase the reinforcing properties of cigarettes. This evidence compellingly shows that manufacturers intend tobacco products to have pharmacological effects and result in addiction.

Tobacco companies have also developed a number of cigarette alternatives. See FINDINGS § II.F.3., infra. In developing cigarette alternatives, the companies have sought to eliminate many of the traditional components and characteristics of cigarettes and cigarette smoke, such as tar and carbon monoxide. Tobacco companies have consistently recognized, however, that cigarette alternatives must deliver adequate amounts of nicotine to satisfy consumers. As a result, most of the alternative cigarette products developed by tobacco companies are simply nicotine delivery systems. For example, R.J. Reynolds has developed two "smokeless cigarettes," Premier and Eclipse. See p. 302 et seq. Nicotine is virtually the only compound (other than the paper and the filter) that is contained in these products in quantities similar to conventional cigarettes. Although these alternative products are very different from one another, they are strikingly the same in their ability to administer a consistent level of nicotine. Industry documents and patents show that other tobacco companies' cigarette alternatives are also intended to be nothing more than nicotine delivery

systems. See pp. 305-07. For example, BATCO developed cigarette alternatives that it characterized as "devices for the controlled administration of nicotine." See p. 307.

A 1970 BATCO R&D conference included a telling illustration of the tobacco industry's recognition of the central importance of nicotine in cigarette alternatives:

> *It was agreed that, if and when total cigarette consumption declined, great opportunities for supplying the demands of other socially acceptable habits could follow. Discussion followed on those opportunities which might arise. Amongst those discussed were a) chewing products, and b) wet snuff [both of which are smokeless tobacco products]. It was felt that this whole area, much of which is already in the tobacco industry, should be examined more thoroughly. Particular attention should be given to buccal administration of nicotine and other physiologically active ingredients. At the same time, it was re-affirmed that we would not contemplate the incorporation of nicotine in edible products.*

See p. 308 (emphasis added). As this passage makes clear, tobacco manufacturers understand that the common feature of cigarettes and smokeless tobacco products is the ability to administer nicotine to consumers, and that the purpose of the nicotine is to produce pharmacological effects in the consumer.

Thus, company documents related to the development of alternatives to both nicotine and conventional tobacco products establish tobacco manufacturers' knowledge that nicotine's psychoactive effects are critical to maintaining a successful market for cigarettes and smokeless tobacco, and that consumers use these products primarily for nicotine's pharmacological effects. The fact that the tobacco industry considers alternative cigarettes that are simply nicotine delivery systems to be functionally equivalent to traditional cigarettes demonstrates that tobacco companies intend their currently marketed tobacco products to be used for pharmacological purposes by consumers.

d. Smokeless Tobacco Manufacturers Manipulate Nicotine Delivery and Foster Graduation of Users From Low to High Nicotine Products.

Smokeless tobacco manufacturers control the delivery of nicotine from smokeless tobacco through a variety of additives and design features. Manufacturers use these additives and features to produce lines of smokeless products that deliver nicotine in increasing amounts. Evidence exists that smokeless tobacco manufacturers employ a "graduation process" to market these products. Low-nicotine products are marketed to new users of smokeless tobacco. After these new users become tolerant to the low-nicotine products, manufacturer marketing encourages smokeless tobacco consumers to "graduate" to higher nicotine products. The goal of the graduation process is to establish and maintain a market for the smokeless tobacco products with the highest nicotine delivery. Smokeless tobacco manufacturers' deliberate manipulation of levels of nicotine delivery, and the marketing of low-nicotine products to new users and high-nicotine products to experienced users, demonstrates the manufacturers' intent to facilitate nicotine addiction. This evidence establishes that smokeless tobacco manufacturers intend to affect the structure and function of the body.

Until the 1970's, smokeless tobacco companies in the United States marketed only products with high nicotine delivery that were not well tolerated by new users and the number of consumers using their products was steadily diminishing. See pp. 279-80. Evidence from the files of smokeless tobacco companies shows that, in the late 1960's or early 1970's, these companies began to entice new users of smokeless tobacco. Id. To do so, they decided to develop low-nicotine products in teabag-like pouches to encourage people to begin using smokeless tobacco. See pp. 280-81. Company documents also reveal that manufacturers

deliberately set out to produce a range of products with low, medium, and high nicotine delivery, see p. 281, and that they understood that nicotine's pharmacological effects were essential to the success of their products. As noted above, the senior vice president for marketing of the largest smokeless tobacco company wrote in a memorandum on new product development that "virtually all tobacco usage is based upon nicotine, 'the kick,' satisfaction." See pp. 186-87.

Analyses, by FDA and others, of current smokeless tobacco products show that smokeless tobacco companies have successfully developed product lines with graduated nicotine deliveries. See p. 276. Abundant evidence exists that manufacturers deliberately manipulate smokeless tobacco products to provide these graduated nicotine deliveries. Smokeless tobacco manufacturers do so primarily by adding various acidic or buffered compounds to the tobacco to alter its "pH," i.e., its relative acidity or alkalinity. See pp. 273-275. By increasing the pH of a product, manufacturers increase the amount of nicotine that is transformed from the "salt" or "bound" form of nicotine into "free nicotine." Only free nicotine can be readily absorbed through the mouths of smokeless tobacco users into the bloodstream. Small adjustments in pH can dramatically raise delivery of free nicotine. For example, raising the salivary pH from 7 to 8 increases the percentage of free nicotine from 10% to 50%, a five-fold increase. See p. 274. Analyses of currently marketed smokeless tobacco products reveal that the "starter" products have a pH in the range of 5 to 7, while the products for experienced users, like Copenhagen, have a pH of 8 or more. The amount of free nicotine delivered from these products correspondingly ranges from 5% to 20% for the starter products and 50% to 80% for the high-end products. See p. 276.

Other features of these products are also designed to lower nicotine absorption at the low (starter) end of the product range and to raise nicotine absorption at the top end. For example, humectants are added to the products to increase moisture content. See p. 279. High moisture content and other design features of smokeless tobacco have the effect of providing an intense "bolus" dose of nicotine to the user when the user first places a wad of tobacco in the mouth. See p. 278. On the other hand, "starter products" like Skoal Bandits are often packaged in a miniature pouch designed to be placed in the user's mouth; the pouch serves to limit the amount of snuff that is placed in the mouth and to create a barrier that decreases the rate of nicotine release from the product. See p. 277. Thus, starter products like Bandit deliver less total nicotine at a slower rate than the high-nicotine products offered by the same companies.

Internal documents from United States Tobacco Co. (UST), the largest smokeless tobacco producer in the United States, demonstrate that the company developed low nicotine snuff products for the specific purpose of creating "starter" products for new users who could not tolerate products with more nicotine. These low-nicotine products were then aggressively marketed to new users through advertising and by offering free samples at college campuses and sports events. See p. 282 et seq. UST documents, including internal memoranda and advertising, demonstrate that smokeless tobacco manufacturers know and intend that their customers will "graduate" upward through the range of nicotine products to the highest nicotine products. For example, a chart prepared by UST's marketing department is labeled "graduation process" and shows a hierarchy of products, with arrows going from Skoal Bandits, to Happy Days and Skoal Long Cuts, and culminating with Copenhagen. See p. 284.

This "graduation" corresponds exactly to the progression of the nicotine levels delivered by the listed products.

The product development and marketing strategies for smokeless tobacco have been extremely successful at recruiting new users. Use of smokeless tobacco products has risen substantially since the 1970's: overall, moist snuff sales almost tripled from 1972 through 1991, while use by male adolescents aged 18 to 19 increased almost 1,500% between 1970 and 1991. See p. 287.

The deliberate marketing of products that deliver graduated amounts of nicotine demonstrates that smokeless tobacco manufacturers know that their products are used to satisfy consumers' desire for increasing amounts of nicotine. The evidence of manipulation of nicotine delivery in smokeless tobacco shows that manufacturers have taken steps to create and sustain the need for nicotine. This evidence is more than sufficient to demonstrate that smokeless tobacco manufacturers intend consumers to become tolerant to, and addicted to, the nicotine in smokeless tobacco. Both tolerance and addiction are effects on the structure and function of the body produced by nicotine. Accordingly, smokeless tobacco products are intended to affect the structure or function of the body.

III. NICOTINE-CONTAINING CIGARETTES AND SMOKELESS TOBACCO PRODUCTS ARE DRUG DELIVERY SYSTEMS THAT ARE APPROPRIATELY REGULATED AS DEVICES.

Nicotine-containing cigarettes and smokeless tobacco products are "intended to affect the structure or any function of the body" within the meaning of the Act's drug and device definitions. 21 U.S.C. §§ 321(g)(1)(C), 321(h)(3). Based on the agency's analysis of the evidence before it: (1) the nicotine in cigarettes and smokeless tobacco products is a drug, achieving its effect through chemical action within the body; (2) cigarettes and smokeless tobacco are drug delivery systems whose purpose is to deliver nicotine in a manner in which it can be most readily absorbed by the consumer, and are, therefore, devices; and (3) cigarettes and smokeless tobacco products are combination products that the agency has the discretion to regulate using drug authorities, device authorities, or a combination of both authorities. 21 C.F.R. § 3.2(e) (1994). The record before the agency supports regulation of cigarettes and smokeless tobacco products pursuant to the Act's device authorities.

FDA considers device-like products, such as instruments, implements, machines, contrivances, implants, or other similar or related articles, 21 U.S.C. § 321(h), whose primary purpose is delivery of a drug, and that are distributed with a drug product, to be drug delivery systems. Intercenter Agreement Between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health § VII.A.1.(b)(October 31, 1991)("Intercenter Agreement"). Examples include contrivances containing drugs, such as pre-filled syringes, transdermal patches, and metered-dose inhalers. Id. Cigarettes and smokeless tobacco products function in a similar manner in that they contain a drug, nicotine; are used to deliver that drug to the site at which the drug will be absorbed into the body, the mouth or lungs; and

after the drug has been delivered, the delivery system, the cigarette butt or smokeless tobacco material, depleted of nicotine, remains and must be disposed of. Only the nicotine delivered by these products achieves its primary intended purpose by chemical action in or on the body.

Specifically, a cigarette is analogous to a metered-dose inhaler, an instrument that converts a drug into an aerosolized form for inhalation and delivery to the lungs for absorption into the bloodstream. Indeed, a cigarette is not simply tobacco, paper, and a filter. It is "a highly engineered product." FDA Docket No. 94P-0069, Response of R.J. Reynolds Tobacco Company, Appendix D, p. 1 (November 2, 1994). A device is an instrument or related article that "does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes." 21 U.S.C. § 321(h).

The primary purpose of parts of the cigarette, each of which is a device or device component within the Act's meaning, and the cigarette itself, a consciously engineered instrument, is to effectuate the delivery of a carefully controlled amount of the nicotine to a site in the human body where it can be absorbed. The drug, nicotine, is generally contained within the treated rolled tobacco. The delivery system, the nicotine-containing cigarette, must be lit to have its intended effect on the structure or function of the body, and, once lit and used, is discarded. When lit, the cigarette produces nicotine-containing smoke, which is inhaled by the consumer and when absorbed in the lungs, yields on average approximately 1.0 mg of nicotine. As the evidence discussed above reveals, cigarettes are drug delivery systems and, accordingly, are devices within the meaning of the Act.

Smokeless tobacco products function like infusion devices or transdermal patches that

deliver a controlled continuous amount of nicotine to the cheek tissue for absorption into the bloodstream. The device element of smokeless products is the tobacco, which contains the nicotine but is not intended to be consumed. Instead, in normal use, most of the tobacco in the product is not absorbed by the user and is removed from the mouth after absorption of the nicotine through the cheek tissue.

The primary purpose of the tobacco is to provide a palpable vehicle that allows nicotine to be extracted from the tobacco by the user's saliva so that it may be absorbed into the body.[13] The tobacco also delivers chemicals added during the manufacturing process, primarily alkalines, that increase the pH within the oral cavity and affect the rate at which the nicotine is absorbed into the body. See FINDINGS § II.E.2.

Because cigarettes and smokeless tobacco products are drug-device combination products, FDA may regulate them as drugs, devices, or both. See 56 Fed. Reg. 58754, 58754-55 (November 21, 1991); Intercenter Agreement § VII.A.1(b). Based on the record before the agency, regulation of cigarettes and smokeless tobacco products pursuant to the Act's device authorities is most appropriate at this time.[14] The alternative, regulating the products

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[13] The fact that smokeless tobacco material is largely organic does not remove it from the definition of a device. FDA regulates many organic substances as devices, as well as liquids and gases. For example, FDA regulates as devices: injectable collagen, hemodialysis fluids, lubricants and lubricating jellies, preservation solutions for organ/tissue transport, absorbable sponges and wound dressings, gas mixtures for pulmonary function tests, spray-on dressings, liquids functioning through physical action applied to the body to cool or freeze tissues, and sodium hyaluronate or hyaluronic acids for use as a surgical aid. See Intercenter Agreement § VII.C.

[14] This decision is similar to the determination of the Department of Health, Education, and Welfare (HEW), before authority over biologic drugs was transferred to FDA, regarding radioactive biologic products. Radioactive biologic products are both biologics under the Public Health Service Act (PHSA), 42 U.S.C. § 262, as well as drugs and new drugs, 21 U.S.C. § 321(g), (p), that may be regulated pursuant to the drug provisions of the FDCA. HEW determined that a drug would not be subject to the new drug provisions of the FDCA if it is a drug regulated as a biologic product pursuant to the licensure provisions of the PHSA. 40 Fed. Reg. 31311, 31312 (July 25, 1975); see 21 C.F.R. § 310.4.

pursuant to the Act's drug authorities, might result in the removal of these products from the market. Over 40 million Americans are currently addicted to cigarettes and smokeless tobacco products. Prohibiting the sale of these products, which could be required if FDA were to apply the Act's new drug authorities to them, could have significant health consequences for a substantial number of these nicotine-addicted consumers. In the unique setting of highly addictive products that have already been marketed for a sufficient period to addict a large number of Americans, application of requirements that could result in the abrupt removal of the products from the market is not the most appropriate regulatory response.

By contrast, the Act's device authorities provide flexible tools that allow FDA to establish and move towards the public health protection goals that are most practicable for cigarettes and smokeless tobacco products. Therefore, FDA is proposing a set of regulatory requirements for these products pursuant to the Act's device authorities.

The Medical Device Amendments of 1976, while having as their objective the ultimate assurance of the safety and effectiveness of marketed devices, contain provisions designed to permit a staged, multi-tiered approach to assuring the safety and effectiveness of long-marketed products. The authorities available under the Act's device provisions may be used to help eliminate or greatly reduce the addiction of the next generation of American children and teenagers to cigarettes and smokeless tobacco products.

Based on the record before the agency, all cigarettes and smokeless tobacco products distributed in the United States are drug-device combination products subject to regulation as devices. The record before the agency includes evidence that these products are intended to

affect the structure or any function of the body, based in part on nicotine's well-established pharmacological and addictive effects and the widespread consumer use of cigarettes and smokeless tobacco for pharmacological purposes. These factors are relevant to establishing the intended use of all brands of cigarettes and smokeless tobacco products distributed in the United States.

The Agency has obtained evidence concerning the knowledge of cigarette and smokeless tobacco product manufacturers about the pharmacological and addictive effects of nicotine in cigarettes and smokeless tobacco, and their manipulation of nicotine delivery to satisfy users' physiological need for nicotine, from the major manufacturers of these products and from CTR. Products from these manufacturers account for the vast majority of the U.S. cigarette and smokeless-tobacco market and probably account for close to 100% of that market. Under FDA's traditional approach to device classification, it is appropriate to classify all marketed cigarettes and smokeless tobacco products as drug delivery devices based on the cumulative evidence obtained from manufacturers.

CONCLUSION

The Food and Drug Administration has conducted an extensive investigation and has engaged in comprehensive analysis regarding the agency's jurisdiction over nicotine-containing cigarettes and smokeless tobacco products. The results of that inquiry and analysis support a finding at this time that nicotine in cigarettes and smokeless tobacco products is a drug, and that these products are drug delivery devices within the meaning of the Federal Food, Drug, and Cosmetic Act. Nonetheless, because the agency recognizes the unique importance of the jurisdictional issue as well as the factual justification for any proposed rule in this area, the agency invites comment on these matters. Comments will receive full and serious consideration.

APPENDIX TO LEGAL ANALYSIS

Examples of FDA's Regulation of Products as Drugs or Devices Based on the Product's Inherent Nature, Actual Use, or Its Effect on the Structure or Function of the Body

FDA has, on a number of occasions, asserted jurisdiction over a product even though the product's labeling and the vendor's advertising or other express representations did not establish that the product was a drug or a device within the meaning of the Act. The agency has found "intended use" and "intended effects" based on the inherent nature of the product, its actual use or effects, or a combination of these factors. Some examples follow:

1. Stimulant Narcotic Chewed or Used as Tea: Beginning in the early 1980's, FDA regulated as unapproved drugs imports of catha edulis, or "khat," a shrub whose leaves act as a stimulant narcotic that affects the central nervous system when chewed or used as tea, even though the agency did not have any information about or claims by vendors. FDA Import Alert 66-23 (March 26, 1982, revised April 2, 1986, and February 9, 1993). FDA issued an import alert for the product, deeming it a drug in the absence of any labeling or other material that would establish intended use. See FDA Import Alert 66-23 (March 26, 1982). FDA initiated a seizure of "khat" in Buffalo in 1985 and the product was ultimately forfeited and destroyed. FDA Import Alert 66-23 (April 2, 1986 revision). Knowledge of khat's use came from United Nations reports and other general sources of information about customs and practices regarding the use of khat. Id.

2. Imitation Cocaine: FDA took numerous enforcement actions in the 1980's against "caine" products that were used to imitate cocaine. "Caine" contained bulk anesthetic powders, such as lidocaine or mannitol, and was often sold as "incense" or "novelty cocaine."

Memorandum from Chief, Prescription Drug Compliance Branch (August 4, 1982), reprinted in Rx Drug Study Bulletin #258. The agency used laboratory analyses of the products, the manner in which the products were offered and sold, such as through magazines not associated with the legitimate drug industry (e.g. the National Enquirer, High Times, Soldier of Fortune, and Easy Rider) and at headshops with other drug paraphernalia, and "street" information that the products provide a "cheap high" to determine the products' intended use. See id. In 1984, the government seized a "caine" product from Golden Rod Music in Dayton, OH. FDC 64350, Case No. C-3-84-686 (S.D. Ohio). The product consisted of more than 25 percent ephedrine, as determined by laboratory analysis. Id. Also in 1984, FDA issued a regulatory letter to Mid-America Drug Co., Evansville, IN., concerning marketing of "caine" products. FDA Administrative File for Mid-America Drug Co., regulatory letter 84-DT-12. The firm voluntarily discontinued sales of the products, as did several other firms that received regulatory letters at about the same time. Id., response to regulatory letter 84-DT-12; see also, FDA Administrative File for Sam's Imports, Dearborn, MI, regulatory letter 85-DT-3 and response; FDA Administrative File for NALPAC, Ltd., Oakpark, MI, regulatory letter 85-DT-5 and response; FDA Administrative File for Tower Enterprises, Ida, MI, regulatory letter 85-DT-2 and response. In 1994, the government prosecuted Edwin and Thomas Dews in Michigan for selling a product called "Milky Trails," labeled as a room odorizer but in fact containing lidocaine. Case No. 94 CR 20040-BC (E.D. Mich.).

3. Hormones in Topical Preparations: The agency has formally taken the position that any statement in the labeling indicating that "hormones" are present in topical products will be considered to be an implied claim for therapeutic purposes, or to affect the structure or

function of the body, and will make the product a drug, even in the absence of more specific claims. 58 Fed. Reg. 47611, 47612 (September 9, 1993); Drug Study Bulletin No. 67 (March 28, 1994); see also 54 Fed. Reg. 40618, 40619 (October 2, 1989). The agency has also taken the position that even in the absence of labeling indicating that "hormones" are present in the product, the mere presence of hormones at levels that affect the structure or any function of the body, or the inclusion of certain hormones that do not have any legitimate cosmetic uses, would be sufficient for a determination that the product is a drug. 58 Fed. Reg. at 47611.

4. Fluoride in Dentifrice Products: FDA considers dentifrice products containing fluoride to be drugs, irrespective of whether any claims are made, because fluoride is widely accepted as an anti-cavity agent by the dental products industry and consumers, and because fluoride affects the structure of the tooth. See 59 Fed. Reg. 6084, 6088 (February 9, 1994); see also 50 Fed. Reg. 39854 (September 30, 1985).

5. Thyroid in Food Supplements: In 1984, the government seized and destroyed a thyroid-containing product that had been marketed as a food supplement by an Arkansas firm. FDC 64270, Case No. B-C-84-61 (E.D. Ark.). FDA had concluded that the product was a drug, based on the recognized effects of thyroid products on the structure and function of the human body.

6. Interferon: In 1983, FDA established a due diligence requirement regarding manufacturers' distribution of interferon, a biologic product composed of proteins. See 48 Fed. Reg. 52644 (November 21, 1983). At the time, interferon could be used only for investigational purposes in laboratory animals and tests in vitro. However, interferon received wide media coverage as a potential "miracle cure" in the treatment of cancer and viral infections in humans.

Because of its concern over diversion of interferon to unapproved uses, the Agency issued the notice to prevent use of interferon in humans.

7. Eye Ailment Device: In the 1960's, FDA undertook an enforcement action against a metal tube containing a light bulb, round metal discs, and colored glass filters used by a medical practitioner in his office in the treatment of various eye malfunctions and conditions. A district court upheld the Agency's conclusion that this use made the tube a device, even though the practitioner made no claims for the product. United States v. An Article of Device . . . Labeled in Part: "Cameron Spitler Amblo-Syntonizer", 261 F. Supp. 243, 245 (D. Neb. 1966).

8. Novelty Condoms: In early 1994, FDA took the position that "novelty condoms" that are usable as condoms would be regulated as condoms even in the absence of express claims (e.g., for birth control or to prevent sexually transmitted diseases). Letter from Ronald Johnson, Director, Office of Compliance, CDRH, to Manufacturers, Distributors, and Importers of Condoms, February 23, 1994. The agency's position was based on the belief that, because of the inherent nature and exclusive use of the article, people would actually use the condoms for prophylactic purposes even though they were not so labeled. The Agency stated that "[l]abeling a functional condom as a novelty is not sufficient" to escape the regulatory requirements applicable to condoms specifically and medical devices in general. Instead, a manufacturer would have to render the product completely unusable as a condom. Id.

9. Noncorrective Tinted Contact Lenses: The agency has taken the position that tinted contact lenses that do not correct or improve vision and are promoted to enhance eye color are medical devices. This position is based on the fact that all contact lenses, including neutral lenses, have a physiological effect on the eye. In 1986, the government obtained a consent

decree of permanent injunction against the sale of a system used to make noncorrective tinted contact lenses on the ground that the system causes adulteration of a medical device, the lenses. FDA INJ 1145, United States v. International Hydron Corp., No. 87-2129 (E.D.N.Y.).

10. Sunscreens: Between 1940 and the 1970's, FDA changed its position regarding the degree to which sunscreens were drugs under the Act. See 58 Fed. Reg. 28194 (May 12, 1993). FDA had stated in a 1940 advisory opinion that a product promoted for the prevention of damage from the sun was a drug while a product promoted for acquiring an even tan was a cosmetic. Id. at 28204. FDA changed its view of the latter category of products, however, because "[s]ince 1940 . . . there has been a significant body of information developed on the harmful effects of the sun on human health and a significant change has occurred in consumer perception of the purpose of suntanning products." Id. FDA explained that sunscreen products affect the structure and function of the body by "altering the normal physiological response to solar radiation," and that consumers expect protection from such products irrespective of the way in which such products are promoted. Id.

11. Tanning Booths: FDA has taken the position that tanning booths are devices under the Act because, by exposing the body to ultraviolet rays, they are intended to affect the structure or function of the body. Based on this position, the Agency has initiated seizure actions in recent years against various tanning booths, including, among others, those in the possession of Chic Wig Boutiques, Clarksville, Indiana. FDC 66099, Case No. NA 91-64-C (N.D. Ind.). The Indiana firm signed a consent decree with regard to this device. Id.; see also FDC 66224 (Chic Tanning Studio, Tampa, Florida), Case No. 92-CV-70829-DT (M.D. Fl.); FDC 65453 (Sunburst Sun Spa, Anchorage, Alaska), Case No. A-87-625-CIV (D. Alaska).

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I. NICOTINE HAS DRUG EFFECTS ON THE BODY

Nicotine is a psychoactive drug that affects the brain, the skeletal muscles, the cardiovascular system, and other systems throughout the body.[15] Psychoactive is defined as having the ability to alter mood, anxiety, behavior, cognitive processes, or mental tension.[16] There is widespread agreement within the scientific community that nicotine causes substantial pharmacological effects, including those that lead to addiction in the majority of users. This section will briefly review: 1) the physiological and central nervous system effects of nicotine; 2) the data that support the conclusion that nicotine is an addictive agent; 3) the evidence that the amount of nicotine in commercially available products is sufficient to cause addiction; and 4) the evidence that consumers use tobacco products for their drug effects.

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[15] U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Nicotine Addiction. Report of the U.S. Surgeon General, 1988.* U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Health Promotion and Education, Office on Smoking and Health. DHHS Publication No. (CDC) 88-8406, 1988. Pages 13-14, 79-124, 410, 596-601. (Hereafter cited as Surgeon General's Report. 1988. *Nicotine Addiction.*)

[16] Hensyl WR, ed. *Stedman's Medical Dictionary.* 25th ed. Baltimore, MD: Williams and Wilkins; 1990:1284.

A. NICOTINE HAS PHYSIOLOGICAL AND CENTRAL NERVOUS SYSTEM EFFECTS

The physiological and central nervous system effects of nicotine involve effects on both the structure and the function of the brain. When it is inhaled in cigarette smoke, nicotine is absorbed into the lungs and then rapidly enters the bloodstream. In smokeless tobacco, it is absorbed through tissues of the mouth or nose and then enters the bloodstream. Once it is in the bloodstream, nicotine crosses the blood-brain barrier and is rapidly distributed to the brain.[17] It is estimated that, once inhaled in cigarette smoke, nicotine reaches the brain in 11 seconds or less.[18] Nicotine generates its effects by binding to receptors in the brain that are intended to receive the neurotransmitter acetylcholine. These receptors, when activated by nicotine, cause the release of other chemicals in the brain that produce effects on mood, alertness, and perhaps cognition. Continued nicotine use causes an increase in the number of receptors that can bind nicotine, and changes the electrical and metabolic activity of the brain.

Nicotine's rewarding effects are the result of its action on a part of the brain called the mesolimbic system, which is also affected by many other addictive drugs.[19] Nicotine, like amphetamine and cocaine, produces its rewarding or reinforcing effects by stimulating the

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[17] Surgeon General's Report. 1988. *Nicotine Addiction.* Page 13.

[18] Benowitz NL. Clinical Pharmacology of Inhaled Drugs of Abuse: Implications in Understanding Nicotine Dependence. *Research Monograph 99.* National Institute on Drug Abuse. 1990. Page 17.

[19] *See:*

Wise RA, Rompre PP. Brain dopamine and reward. *Ann Rev Psychol.* 1989;40:191-225.

Clarke PBS. Mesolimbic dopamine activation--the key to nicotine reinforcement? *The Biology of Nicotine Dependence.* Wiley, Chichester (Ciba Foundation Symposium 152) 1990;153-168.

release of dopamine, a chemical produced in the mesolimbic system. Dopamine plays a major role in regulating pleasurable sensations.[20] (See Appendix 1 for a summary of the studies indicating that nicotine acts on the mesolimbic dopaminergic system.)

Nicotine produces a range of other complex pharmacological effects that are related to its dose and/or bioavailability. For example, at low doses, nicotine stimulates the cardiovascular system, producing an increase in blood pressure and heart rate. At higher doses or more rapid administration, nicotine slows the heart rate.[21]

Depending on the circumstances, nicotine delivered by cigarette smoking can have an arousal-increasing or arousal-reducing effect.[22] These effects have been confirmed using electroencephalographic (EEG) analysis.[23] When smokers are placed in a stressful situation,

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[20] *See:*
Pomerleau OF, Pomerleau CS. Neuroregulators and the reinforcement of smoking: towards a biobehavioral explanation. *Neurosci Biobehav Rev.* 1984;8:503-513.

Wise and Rompre, note 19, *supra,* at pp. 191-225.

Clarke, note 19, *supra,* at pp. 153-168.

[21] Henningfield JE, Miyasato K, Jasinski DR. Abuse liability and pharmacodynamic characteristics of intravenous and inhaled nicotine. *J. Pharmacol Exp Ther.* 1985;234:1-12.

[22] Norton R, Brown K, Howard R. Smoking, nicotine dose and the lateralisation of electrocortical activity. *Psychopharmacology.* 1992;108:473-479.

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

Pritchard WS. Electroencephalographic effects of cigarette smoking. *Psychopharmacology.* 1991;104:485-490.

Golding JF. Effects of cigarette smoking on resting EEG, visual evoked potentials and photic driving. *Pharmacology Biochemistry and Behavior.* 1988;29:23-32.

smoking can have a depressant effect on the EEG profile.[24] When smokers are under conditions of low arousal induced by mild sensory isolation, cigarette smoking can have a stimulant effect.[25] In other words, smoking appears to have a relaxing effect in stressful situations and a stimulating effect in otherwise nonstimulating circumstances.

Smoking or the administration of nicotine appears to have mixed results in its effects on sustained attention.[26] The tobacco industry has conducted several studies on nicotine's effect on performance and cognition. While some studies showed increased performance and response,[27] others showed little or no effect.[28] Many of these studies were conducted with nicotine-deprived subjects, and the results may reflect the reversal of deficiencies caused by nicotine withdrawal. The 1988 Surgeon General's Report concluded that "[a]fter smoking cigarettes or receiving nicotine, smokers perform better on some cognitive tasks . . . than they do when deprived of cigarettes or nicotine. However, smoking and nicotine do not improve general learning."[29] (An extensive discussion of the physiological and central nervous system

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[24] *See* Pritchard, note 23, *supra,* at pp. 485-490.

[25] Golding J, Mangan GL. Arousing and de-arousing effects of cigarette smoking under conditions of stress and mild sensory isolation. *Psychophysiology.* 1982;19(4):449-56.

[26] Heishman SJ, Taylor RC, Henningfield JE. Nicotine and smoking: A review of effects on human performance. *Experimental and Clinical Psychopharmacology.* 1994;2(4):345-395.

[27] *See:*
Wesnes K, Warburton DM. Effects of smoking on rapid information processing performance. *Neuropsychobiology.* 1983;9:223-229.

Wesnes K, Warburton DM. Effects of scopolamine and nicotine on human rapid information processing performance. *Psychopharmacology.* 1984;82:147-150.

[28] *See* Heishman et al, note 26, *supra.*

[29] Surgeon General's Report. 1988. *Nicotine Addiction.* Page 441.

effects of nicotine is available in the 1988 Surgeon General's Report.[30])

[30] *Id.* at pp. 381-458.

B. NICOTINE IS ADDICTIVE

1. Major Public Health Groups and Leading Experts Concur

Until the 1980's, nicotine was not widely appreciated to be an addictive drug. Within the past 15 years, however, broad international agreement has developed within the scientific community that nicotine in tobacco is a highly addictive or dependence-producing substance. The terms "addictive" and "dependence-producing" are generally used interchangeably; both terms refer to the persistent and repetitive intake of psychoactive substances despite evidence of harm and a desire to quit.[31] Some scientific organizations have replaced the term "addictive" with "dependence-producing" to shift the focus to dependent patterns of behavior and away from the moral and social issues associated with addiction.[32] Both terms are equally relevant for purposes of understanding the drug effects of nicotine, and in this section, the terms will be used interchangeably. The current broad recognition that nicotine is an addictive substance has been due to: 1) an evolution in the understanding of the science of addiction (e.g., the recognition that a substance does not have to be intoxicating when used at addictive levels);[33] 2) epidemiological evidence establishing the high percentage of tobacco

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[31] Surgeon General's Report. 1988. *Nicotine Addiction.* Page 7.

[32] *Id.* at p. 11.

[33] U.S. Public Health Service. *Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service.* U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control. PHS Publication No. 1103, 1964. (Hereafter cited as Surgeon General's Report. 1964. *Smoking and Health.*) The 1964 Surgeon General's Report considered nicotine to be "habituating" rather than addictive because it did not appear to produce intoxication or cause physical dependence, and its users did not tend to increase the dose. These were considered to be the features of addictive drugs.

At that time, cocaine and amphetamines were also regarded as not causing physical dependence. *See:*

Wesson DR, Smith DE. Cocaine: Its Use for Central Nervous System Stimulation Including Recreational

users who display the clinical symptoms of addiction; and 3) the accumulation of evidence in the last two decades demonstrating, in both laboratory animals and humans, that nicotine is a psychoactive drug that produces pharmacological effects similar to those seen with other addictive substances.

Scientists' understanding of addiction has evolved over the past 30 years. Earlier definitions of addiction suggested that addiction was predominately the result of weakness in the personality of the user rather than the result of the pharmacological effects of the addicting substance.[34] More recently, animal and human research has revealed the pharmacological basis of addiction.[35] It has been shown that addictive substances produce

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and Medical Uses. In: Cocaine: 1977. NIDA Research Monograph. DHEW Publication Number (ADM) 77-471. Department of Health, Education, and Welfare. Rockville, MD. 1977. Page 145.

Winkler A. The Etiology of Opioid Dependence. In: Opioid Dependence: Mechanisms and Treatment. Winkler A (ed). 1980. Plenum Press. New York, NY. Page 26.

Winkler A. The Problems of Drug Dependence. In: Opioid Dependence, *supra*, at p. 13.

[34] *See:*

The Committee on Nomenclature and Statistics of the American Psychiatric Association. 1952. *Diagnostic and Statistical Manual, Mental Disorders with Special Supplement on Plans for Revision.* American Psychiatric Association. Washington, DC. Page 39.

Surgeon General's Report. 1964. *Smoking and Health.* Page 351.

Surgeon General's Report. 1988. *Nicotine Addiction.* Page 248.

[35] *See:*

Hanson HM, Ivester CA, Morton BR. Nicotine self-administration in rats. In: *Cigarette Smoking as a Dependence Process, NIDA Research Monograph 23.* U.S. Department of Health, Education, and Welfare. 1979. Pages 70-90.

Goldberg SR, Spealman RD, Goldberg DM. Persistent behavior at high rates maintained by intravenous self-administration of nicotine. *Science.* 1981;214:573-575.

Griffiths RR, Henningfield JE, Bigelow GE. Human cigarette smoking: manipulation of number of puffs per bout, interbout interval and nicotine dose. *J Pharmacol Exp Ther.* 1981;220(2):256-265.

definable chemical effects in the brain that reinforce continued use of these substances and cause physiological and/or psychological dependence on these substances.[36] The contemporary understanding of addiction also places a major emphasis on the intrinsic pharmacological ability of a substance to cause compulsive, regular use and on the inability of users to stop using the substance, even when they are strongly motivated to do so.[37]

In 1986, the Office of the U.S. Surgeon General issued a report concluding that nicotine in smokeless tobacco is addictive.[38] In 1988, the Surgeon General issued an additional report concluding that nicotine in cigarettes and other forms of tobacco is addictive.[39]

The landmark 1988 report by the Surgeon General ("the 1988 report") noted that the

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Griffiths RR, Henningfield JE. Pharmacology of cigarette smoking behavior. *Trends Pharmacol Sci.* 1982;3:260-263.

Henningfield JE, Goldberg SR. Nicotine as a reinforcer in human subjects and laboratory animals. *Pharmacol Biochem Behav.* 1983;19(6):989-992.

[36] Surgeon General's Report. 1988. *Nicotine Addiction.* Pages 170-279.

[37] *See:*
American Psychiatric Association. 1994. *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition).* American Psychiatric Association. Washington, DC. Page 176. (Hereafter cited as American Psychiatric Association. 1994. *DSM IV.*)

World Health Organization. 1992. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines.* World Health Organization. Geneva, Switzerland. Page 76. (Hereafter cited as World Heath Organization. 1992. *ICD-10.*)

Surgeon General's Report. 1988. *Nicotine Addiction.* Pages 248-250.

[38] U.S. Department of Health and Human Services. *The Health Consequences of Using Smokeless Tobacco: A Report of the Advisory Committee to the Surgeon General, 1986.* U.S. Department of Health and Human Services, Public Health Service, Bethesda, MD. NIH Publication No. 86-2874, April 1986. Pages 144-145, 166. (Hereafter cited as Surgeon General's Report. 1986. *Smokeless Tobacco.*)

[39] Surgeon General's Report. 1988. *Nicotine Addiction.* Page 9.

main features of the definitions of addiction used by groups throughout the world are highly consistent. The 1988 report adopted a set of criteria based on the common criteria of these definitions. The primary criteria for drug dependence relied on in the Surgeon General's Report were:

1. highly controlled or compulsive use (even despite a desire, or repeated attempts, to quit);
2. psychoactive ("mood altering") effects produced by the action of the drug substance on the brain; and
3. drug-motivated behavior caused by "reinforcing" effects of the psychoactive substance.[40]

The 1988 report identified the following additional criteria for identifying drug dependence:

- repetitive and stereotyped patterns of use;
- persistent use despite adverse physical, social or psychological effects;
- quitting episodes followed by relapse;
- recurrent cravings for the drug, especially during abstinence;
- development of tolerance (diminished responsiveness to the drug's effects, sometimes accompanied by increased intake);
- withdrawal symptoms that can motivate further use of the drug; and
- pleasant (euphoriant) effects produced by the drug.[41]

The 1988 report exhaustively reviewed the available data on the effects of nicotine on the body, the metabolism of nicotine within the body, the dependence-producing properties of

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[40] *Id.* at p. 7.

[41] *Id.* at pp. 7-8.

nicotine, tobacco use compared to other drug dependencies, the pharmacological effects of nicotine that promote tobacco use, and treatment of tobacco dependence. Applying the criteria for drug dependence listed above to these data, the 1988 Surgeon General's Report concluded that:

1. Cigarettes and other forms of tobacco are addicting;

2. Nicotine is the drug in tobacco that causes addiction; and

3. The pharmacological and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine.[42]

Major public health organizations and leading experts have concluded that nicotine is an addictive or dependence-producing substance.

- The World Health Organization, the American Medical Association, the American Psychiatric Association, the American Psychological Association, the Royal Society of Canada, and the Medical Research Council in the United Kingdom have all recognized that nicotine is an addictive or dependence-producing drug.[43]

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[42] *Id.* at pp. 6-9.

[43] *See:*

World Health Organization. 1974. *World Health Organization Technical Report Series No. 551. WHO Expert Committee on Drug Dependence, Twentieth Report.* World Health Organization. Geneva, Switzerland. Pages 15-16.

World Health Organization. 1992. *ICD-10.* Page 324.

American Medical Association. *1993 AMA Policy Compendium. Ethyl alcohol and nicotine as addictive drugs.* American Medical Association. 1993.

American Psychiatric Association. 1980. *Quick Reference to the Diagnostic Criteria from DSM-III.* American Psychiatric Association. Washington, DC. Page 99.

American Psychological Association. Statement of the American Psychological Association before the U.S. House of Representatives, Committee on Energy and Commerce, Subcommittee on Health and the Environment on the subject of The 1988 Surgeon General's Report, *The Health Consequences of*

- On August 2, 1994, FDA's Drug Abuse Advisory Committee, an independent group composed primarily of experts on addiction science, concluded that cigarettes and other forms of tobacco are addicting, and that nicotine is the drug in tobacco that causes addiction. The FDA advisory committee also concluded that all currently marketed cigarettes contained addicting levels of nicotine.
- In a 1991 survey, the vast majority of scientists funded by the tobacco industry stated that they believed that cigarette smoking is addictive.[44] According to this report, among the principal investigators of research projects funded by the tobacco industry in 1989, 83.3% strongly agreed and 15.3% agreed somewhat that cigarette smoking is addictive.[45]

Furthermore, the medical community has, since the early 1980's, come to recognize that nicotine addiction is a clinical disorder. The Diagnostic and Statistical Manual of Mental Disorders (DSM), published by the American Psychiatric Association, and the International Statistical Classification of Disease and Related Health Problems (ICD), published by the

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Smoking: Nicotine Addiction. July 29, 1988. Page 1.

Royal Society of Canada. *Tobacco, Nicotine, and Addiction: A Committee Report.* Prepared at the request of The Royal Society of Canada for The Health Protection Branch, Health and Welfare Canada. August 31, 1989. Pages 8-9.

Medical Research Council. The Basis of Drug Dependence. *MRC Field Review.* Medical Research Council. 1994. Page 11.

[44] Cummings KM, Sciandra R, Gingrass A, Davis R. What scientists funded by the tobacco industry believe about the hazards of cigarette smoking. *Am. J of Pub Health.* 1991;81(7)894.

[45] *Id.* at p. 895.

World Health Organization, use very similar criteria to identify dependence.[46] Like the criteria specified by the U.S. Surgeon General, these criteria emphasize the ability of a substance to produce compulsive use, withdrawal and/or tolerance, inability to control or terminate drug use despite efforts to quit or reduce use, and continued use despite harmful effects. (See Appendix 1 for a description and history of the criteria for identifying addiction.)

Nicotine has been recognized as dependence-producing under the DSM criteria since 1980. The most recent version of DSM (DSM-IV) recognizes two substance use disorders

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[46] The most recent version of DSM (DSM-IV) defines "substance dependence" as substance use that produces three or more of the following symptoms in users:

- marked tolerance;
- a withdrawal syndrome and/or the substance is taken to relieve or avoid withdrawal symptoms;
- the substance is often taken in larger amounts over a longer period of time than intended;
- persistent desire or unsuccessful efforts to cut down or control substance use;
- a great deal of time spent in activities necessary to obtain the substance, use the substance (e.g., chain smoking), or recover from its effects;
- important social, occupational, or recreational activities are given up or reduced because of substance use; and
- use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

DSM-IV explains how the following criteria are apparent in nicotine dependence: tolerance, withdrawal, desire to quit, great deal of time using, and continued use despite medical problems. American Psychiatric Association. 1994. *DSM IV.* Pages 181, 243.

"Dependence syndrome" is characterized under the ICD-10 as a cluster of effects after repeated use of a substance resulting in three or more of the following symptoms:

- a strong desire or sense of compulsion to take the substance;
- an impaired capacity to control substance-taking behavior in terms of its onset, termination, or levels of use;
- substance use with the intention of relieving withdrawal symptoms and with awareness that this strategy is effective;
- a physiological withdrawal state;
- evidence of tolerance such that the increased doses of the substance are required in order to achieve effects originally produced by lower doses;
- progressive neglect of alternative pleasures or interests in favor of the substance; and
- persisting with substance use despite clear evidence of overtly harmful consequences.

World Health Organization. 1992. *ICD-10.* Pages 75-76, 321.

associated with nicotine: nicotine dependence and nicotine withdrawal.[47]

The ICD has included tobacco as a dependence-producing substance since 1992. Previously, the ICD recognized the existence of tobacco dependence, but tobacco was treated separately from other addictive drugs because tobacco differed in its psychotoxic effects[48] when used at usual doses. With the publication of ICD-10 in 1992, however, tobacco was included with the other addictive drugs.[49]

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[47] *See* American Psychiatric Association. 1994. *DSM IV,* note 37, *supra,* at p. 99. An individual is classified as having physiologic (in addition to psychological) dependence on a substance under DSM-IV if there is evidence of tolerance to or withdrawal from the substance. *Id.*

[48] World Health Organization. 1978. *Mental Disorders: Glossary and Guide to Their Classification in Accordance with the Ninth Revision of the International Classification of Diseases.* World Health Organization. Geneva, Switzerland. Page 43.

[49] World Health Organization. 1992. *ICD-10.* Page 75.

2. Epidemiological Data Establishes That Tobacco Users Display the Clinical Symptoms of Addiction

a. Studies Documenting Symptoms of Addiction in Smokers

Population studies of smokers conducted in recent years clearly demonstrate that nicotine produces regular, compulsive use, that such use is persistent despite both attempts to quit and an appreciation of cigarette's harmful effects, and that abstinence from nicotine produces withdrawal symptoms:

Regular, compulsive use:

- 87% of people who smoke cigarettes smoke every day;[50] and
- Nearly two-thirds of smokers have their first cigarette within the first half-hour after they wake up.[51]

Use persists despite attempts to quit or reduce use:

- In one study, 84.3% of those who smoked a pack or more per day had unsuccessfully tried to reduce the number of cigarettes smoked.[52]
- A smoker who makes a serious attempt to stop smoking has a less than 5% chance of being off cigarettes a year later;[53]
- Each year in the United States, 15 million people try to quit smoking, but less than 3%

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[50] Centers for Disease Control. *1991 National Health Interview Survey.* Atlanta, GA. U.S. Department of Health and Human Services, 1991.

[51] Centers for Disease Control. *1987 National Health Interview Survey.* Atlanta, GA. U.S. Department of Health and Human Services, 1987.

[52] Henningfield JE, Clayton R, Pollin W. Involvement of tobacco in alcoholism and illicit drug use. *British Journal of Addiction.* 1990;85:280.

[53] Sachs DPL, Leischow SJ. Pharmacologic Approaches to Smoking Cessation. *Clinics in Chest Medicine.* 1991;12(4):788.

have long-term success;[54]

- In one study, 70% of current smokers reported they would "like to completely stop smoking";[55] and
- 83% to 87% of cigarette smokers who smoke more than 26 cigarettes a day believe they are addicted.[56]

Use persists despite harmful consequences:

- In one survey, 90% of smokers agreed with the general proposition that smoking is harmful to health, 65% believed that smoking had already affected their health, and 77% believed that they could avoid or decrease serious health problems by quitting smoking;[57]
- Almost half of the smokers who undergo surgery for lung cancer resume smoking;[58] and
- Even after smokers have had their larynxes removed, 40% try smoking again.[59]

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[54] Centers for Disease Control. *Morbidity and Mortality Weekly Report.* "Cigarette Smoking Among Adults-United States, 1993." December 23, 1994. Page 927.

[55] *Id.*

[56] Substance Abuse and Mental Health Services Administration. *1991/1992 National Household Survey on Drug Abuse.* U.S. Department of Health and Human Services.

[57] Thomas RM, Larsen MD. *Smoking prevalence, beliefs, and activities by gender and other demographic indicators.* Princeton, NJ. The Gallup Organization, Inc. 1993.

[58] Davison G, Duffy M. Smoking habits of long term survivors of surgery for lung cancer. *Thorax.* 1982;37:331-333.

[59] West R, Himbury S. Smoking habits after laryngectomy. *Br Med J.* 1985;291:514-515.

Abstinence produces withdrawal symptoms:

- Abstinence from smoking is often accompanied by powerful cravings for a cigarette;[60]
- Smokers in a position to compare the effects of nicotine with the effects of other addictive drugs say they are comparable;[61] and
- Nicotine replacement therapy significantly reduces withdrawal symptoms in smokers who are attempting to quit.[62]

Data from clinical research evaluating nicotine replacement therapy (nicotine gum and patches) as aids in smoking cessation support the conclusion that a high proportion of smokers are addicted. The studies, submitted to the FDA as part of new drug applications for nicotine replacement products, were conducted in male and female smokers who smoked about a pack to a pack and a half of cigarettes (about 20 to 30 cigarettes) per day. The subjects were recruited from the general population by advertisement, from primary health care settings, and from medically based smoking cessation programs.[63]

Participants in these studies clearly demonstrated addiction to nicotine delivered from cigarettes. All reported symptoms of nicotine addiction at trial entry, and all suffered withdrawal symptoms after smoking cessation. These withdrawal symptoms were relieved

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[60] *See:*
Benowitz NL. Cigarette smoking and nicotine addiction. *Medical Clinics of North America.* 1992;76(2):423.

West R, Schneider N. Craving for Cigarettes. *British Journal of Addiction.* 1987;82:407.

[61] Henningfield JE, Miyasato K, Jasinski DR. Abuse liability and pharmacodynamic characteristics of intravenous and inhaled nicotine. *J Pharmacol Exp Ther.* 1985;234(1):4-5.

[62] NDA 20-076 Habitrol (Ciba), NDA 20-150 Nicotrol (Kabi), NDA 19-983 ProStep (Elan), NDA 20-165 Nicoderm (Alza), NDA 20-066 Nicorette (Merrell Dow).

[63] *Id.*, NDA's for Habitrol (Ciba), ProStep (Elan), and Nicoderm (Alza).

entirely or partly by medical administration of nicotine.

Smokers using the above nicotine replacement products (in the dosage range of 14 to 24 mg/nicotine per day) had an initial quit rate of about 50%, twice that of smokers receiving placebo. This two-fold difference was maintained throughout a full year of follow-up, and was associated with reductions in craving, withdrawal symptoms, and the desire to smoke.[64] In studies in which nicotine replacement therapy was provided for a year or more, relapse rates were nearly half those of studies in which nicotine replacement was halted after a fixed interval (usually about 6 to 12 weeks).[65]

Data from these studies demonstrate how tenacious nicotine addiction is, even for adults who express a strong desire to quit smoking and who receive optimal medical care. Only half of the patients studied were able to stop smoking for as long as 1 week, and the long-term failure rate was more than 80% after patients were withdrawn from nicotine replacement. The fact that nicotine replacement therapy in smokers reduces relapse rates provides strong evidence that it is the nicotine in tobacco products that creates and sustains addiction to cigarettes.

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[64] *See:*
Fiore MC, Smith SS, Jorenby DE, Baker TB. The effectiveness of the nicotine patch for smoking cessation: a meta-analysis. *JAMA.* 1994;271(24):1940-47.

NDA 20-076 Habitrol (Ciba), NDA 20-150 Nicotrol (Kabi), NDA 19-983 ProStep (Elan), NDA 20-165 Nicoderm (Alza), NDA 20-066 Nicorette (Merrell Dow).

[65] *Id.*

b. Studies Documenting Symptoms of Addiction in Smokeless Tobacco Users

Smokeless tobacco users can also develop a dependence on nicotine similar to that experienced by cigarette smokers.[66] The Surgeon General's 1986 report concluded that smokeless tobacco is addictive.[67] This is not surprising, since smokeless tobacco users can absorb at least as much nicotine as smokers.[68] The 1986 report states that:

> *. . . given the nicotine content of smokeless tobacco, its ability to produce high and sustained blood levels of nicotine, and the well-established data implicating nicotine as an addictive substance, one may deduce that smokeless tobacco is capable of producing addiction in users.*[69]

Studies have shown that smokeless tobacco is associated with compulsive use,[70] persistent use despite efforts to quit,[71] persistent use despite harmful consequences,[72] and

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[66] Benowitz NL. Pharmacology of smokeless tobacco use: nicotine addiction and nicotine-related health consequences. In: *Smokeless Tobacco or Health, An International Perspective.* Smoking and Tobacco Control, Monograph 2. U.S. Department of Health and Human Services. Public Health Service. National Institutes of Health. NIH Publication No. 93-3461. 1993. Page 227.

[67] Surgeon General's Report.1986. *Smokeless Tobacco.* Pages 182-183.

[68] Surgeon General's Report. 1994. *Preventing Tobacco Use Among Young People.* Page 40.

[69] *Id.* at p. 141.

[70] *See* Benowitz, note 66, *supra,* at p. 223.

[71] *See:*
Ary DV, Lichtenstein E, Severson HH, Weissman W, Seeley JR. An in-depth analysis of male adolescent smokeless tobacco users: interview with users and their fathers. *J. Behavioral Medicine.* 1989;12:449-467.

Severson HH. Enough snuff: ST cessation from the behavioral, clinical, and public health perspectives. In: *Smokeless Tobacco or Health, An International Perspective.* Smoking and Tobacco Control, Monograph 2. U.S. Department of Health and Human Services. Public Health Service. National Institutes of Health. NIH Publication No. 93-3461. 1993. Pages 281-282.

[72] Connolly GN, Winn DM, Hecht SS, Henningfield JE, Hoffman D, Walker B. The re-emergence of smokeless tobacco. *N. Engl J. Med.* 1986;314(16):1020-1026.

withdrawal symptoms when use is discontinued.[73,74]

Fewer clinical and epidemiological data are available on the prevalence of addiction among smokeless tobacco users than among smokers. However, some users of smokeless tobacco products do meet addiction criteria.[75] A 1986 report of the Office of the Inspector General of the Department of Health and Human Services found that 37% of young users of smokeless tobacco (also called "spit" tobacco) continue use because they are addicted.[76] In a study involving 675 men enrolled in a cessation program, 68% reported an average of four unsuccessful attempts to quit.[77] Other studies of smokeless tobacco cessation programs reveal that many users continue consuming the product despite their desire to quit.[78] Glover reported a 2.3% quit rate at 6 months and concluded that smokeless tobacco may be more addicting than cigarette smoking.[79] Other researchers have found that over one-third of the current

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[73] Hatsukami D, Gust W, Keenan R. Physiologic and subjective changes from smokeless tobacco withdrawal. *Clin Pharmacol Ther.* 1987;41(1):103-107.

[74] *Id.*

See also Severson, note 71, *supra,* at p. 282.

[75] Benowitz NL. Pharmacology of Smokeless Tobacco Use: Nicotine Addiction and Nicotine-Related Health Consequences. In: *Smokeless Tobacco or Health,* Smoking and Tobacco Control Monograph 2. U.S. Department of Health and Human Services.1993. Page 224.

[76] U.S. Department of Health and Human Services. *Spit Tobacco and Youth.* Washington DC. U.S. Department of Health and Human Services, Office of the Inspector General. 1992. Page 7.

[77] *See* Severson, note 71, *supra,* at pp. 281-282.

[78] *See:*
Glover ED. Conducting smokeless tobacco cessation clinics. *Am. J. Pub. Health.* 1986;76(2):207.

Hatsukami D, Nelson R, Jensen J. Smokeless tobacco: Current status and future directions. *Brit. J. of Addiction.* 1991;86:559-563.

[79] *See:*
Glover ED, Glover PN. Smokeless tobacco cessation and nicotine reduction therapy. In: *Smokeless*

smokeless tobacco users report an unsuccessful attempt to quit, despite the fact that 92% of those surveyed believed that there are health risks associated with smokeless tobacco use.[80]

Studies suggest that tolerance to nicotine develops with prolonged smokeless tobacco use. One study noted that a higher percentage of older users of smokeless tobacco used brands with a higher nicotine content compared with younger users.[81] A World Health Organization study group reported on another study that showed a positive relationship between the number of years of smokeless tobacco use, the number of minutes per day of reported use, and urinary nicotine and cotinine[82] levels. These relationships are consistent with the development of tolerance and physical dependence.[83]

Biglan and coworkers demonstrated that nicotine reinforces smokeless tobacco use. In one study that describes the drug-reinforcing behavior of the product, smokeless tobacco users were found to titrate the level of nicotine in their bodies by adjusting use to maintain a specified level of nicotine. In another study in which men used both snuff and cigarettes, the subjects smoked more cigarettes when smokeless tobacco use was restricted, and consumed

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Tobacco or Health, An International Perspective. Smoking and Tobacco Control, Monograph 2. U.S. Department of Health and Human Services. Public Health Service. National Institutes of Health. NIH Publication No. 93-3461. 1993. Pages 291-295.

Glover, note 78, *supra,* at p. 207.

[80] *See* Ary, note 71, *supra.*

[81] Browson RC, DiLorenzo TM, Van Tuinen M, Finger WW. Patterns of cigarette and smokeless tobacco use among children and adolescents. *Preventive Medicine.* 1990;19:170-180.

[82] Cotinine is a major metabolite of nicotine and an indicator of nicotine absorption.

[83] World Health Organization. 1988. *WHO Technical Report Series No 773. Smokeless Tobacco Control: Report of a WHO Study Group.* World Health Organization. Geneva, Switzerland. Page 36.

more smokeless tobacco when cigarette use was restricted.[84]

Smokeless tobacco users who are addicted experience withdrawal symptoms similar to those reported by smokers.[85] One study found that among daily smokeless tobacco users ages 10 to 22 who had previously tried to quit, 93.3% experienced at least one symptom of nicotine withdrawal.[86] It has been concluded that "dependence on smokeless tobacco may be no less tenacious than dependence on cigarettes."[87] (See Appendix 1 for a more complete discussion of the definition of addiction and rates of dependence.)

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[84] *See* Benowitz, note 66, *supra,* at pp. 223-224.

[85] *See:*
Hatsukami, note 73, *supra,* at pp.103-107.

Severson, note 71, *supra,* at p. 282.

[86] U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention. Reasons for tobacco use and symptoms of nicotine withdrawal among adolescents and young adult tobacco users--United States, 1993. *MMWR.* 1994;43(41):745-750.

[87] Jarvis MJ. Dependence on smokeless tobacco. In: *Smokeless Tobacco or Health, An International Perspective.* Smoking and Tobacco Control, Monograph 2. U.S. Department of Health and Human Services. Public Health Service. National Institutes of Health. NIH Publication No. 93-3461. 1993. Page 243.

3. Laboratory Studies Establish That Nicotine Produces Pharmacological Effects Similar to Those of Other Addictive Substances

Evidence gathered in the last two decades demonstrates, in both laboratory animals and humans, that nicotine is a psychoactive drug that produces pharmacological effects similar to those of other addictive substances. Many of the advances in the understanding of the psychopharmacological and addictive aspects of nicotine have come from recent laboratory studies using both animals and human volunteers.

Animal studies have the advantage of being able to assess the pharmacological actions of a potentially addictive substance, independent of such factors as the taste of the substance, the personality of the user, or social factors such as peer pressure. Studies using human volunteers have the advantage of allowing the subject to directly inform the researcher of the subjective effects of the drug being studied.

Two kinds of studies are used to determine whether a substance may be an addictive drug: "drug discrimination" studies and "self-administration" studies. There is a strong correlation between the results of these studies in animals and humans. Substances that animals identify as similar to known psychoactive drugs in drug discrimination studies and substances that animals self-administer in self-administration studies are highly likely to be addictive in humans. With very few exceptions, substances that are addictive in humans are self-administered by animals.[88]

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[88] Gardner EL. Brain Reward Mechanism. In: *Substance Abuse, A Comprehensive Textbook.* 2nd ed. Baltimore, MD: Williams and Wilkins; 1992:70.

a. Animal studies

An impressive number of animal studies have demonstrated that nicotine has pharmacological properties common to many other addictive drugs. These studies establish that nicotine, like other addictive drugs, has psychoactive properties that exert control over behavior.

(i) Drug Discrimination Studies

Drug discrimination studies are used to evaluate the subjective effects (discriminative stimulus properties) of a drug and to make direct comparisons of these effects to known dependence-producing drugs.[89] The ability of a substance to produce discriminative stimulus effects is one characteristic of an addictive substance. In drug discrimination studies, animals identify nicotine as having a highly specific discriminative stimulus profile and some similarity with the discriminative stimulus effects of cocaine and amphetamine.[90] (See

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[89] Balster RL. Drug abuse potential evaluation in animals. *Br J Addiction.* 1991; 86:1549-1588.

[90] *See:*

Takada K, Swedberg MDG, Goldberg SR, Katz JL. Discriminative stimulus effects of intravenous l-nicotine and nicotine analogs or metabolites in squirrel monkeys. *Psychopharmacology.* 1989;99:208-212.

Pratt JA, Stolerman IP, Garcha HS, Giardini V, Feyerabend C. Discriminative stimulus properties of nicotine: Further evidence for mediation at a cholinergic receptor. *Psychopharmacology.* 1983;81:54-60.

Goldberg SR, Risner ME, Stolerman IP, Reavill C, Garcha HS. Nicotine and some related compounds: effects on schedule-controlled behaviour and discriminative properties in rats. *Psychopharmacology.* 1989;97:295-302.

Chance WT, Murfin D, Krynock GM, Rosecrans JA. A description of nicotine stimulus and tests of its generalization to amphetamine. *Psychopharmacology.* 1977;55:19-26.

Stolerman IP, Garcha HS, Pratt JA, Kumar R. Role of training dose in discrimination of nicotine and related compounds by rats. *Psychopharmacology.* 1984;84:413-419.

Appendix 1 for a summary of the studies documenting nicotine's discriminative stimulus effects and the site of these actions.)

(ii) Self-Administration

The self-administration model is widely used to assess a drug's ability to induce and maintain drug-seeking behavior in animals.[91] Self-administration studies determine whether animals will press a lever to give themselves repeated doses of the test substance. The ability of a substance to cause self-administration in animals demonstrates that the substance is a positive reinforcer; i.e., that it induces continued, compulsive use.[92] As noted above, having a positive reinforcing effect in animals is one of the key pieces of predictive evidence that a substance will produce addiction in humans.

Like many addictive drugs, such as cocaine, opiates, and hypnotics, nicotine has now been demonstrated through self-administration studies to be an effective positive reinforcer in animals.[93] This property of nicotine was not consistently demonstrated until the 1980s, when

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Stolerman IP. Discriminative stimulus effects of nicotine in rats trained under different schedules of reinforcement. *Psychopharmacology*. 1989;97:131-138.

[91] *See:*
Schuster CR, Thompson T. Self-administration of behavioral dependence on drugs. *Annual Rev of Pharm.* 1969;9:483-502.

Griffiths RR, Bigelow GE, Henningfield JE. Similarities in animal and human drug-taking behavior. *Advances in Substance Abuse*. 1980;1:1-90.

[92] *See*:
Schuster, note 91, *supra,* at pp. 483-502.

Griffiths, note 91, *supra,* at pp. 1-90.

[93] *See:*
Cox BM, Goldstein A, Nelson WT. Nicotine self-administration in rats. *British Journal of*

it was discovered that the reinforcing efficacy of nicotine is highly dependent on the schedule by which the drug is made available to the animals and the specific amount administered.[94] Intermittent availability of nicotine, which parallels the pattern of cigarette smoking, will induce self-administration in animals, while continuous administration (which was used in the earlier studies) is far less likely to do so. (See Appendix 1 for a summary of the studies establishing that nicotine is a positive reinforcer in animal self-administration studies.)

b. Studies in Human Volunteers

In addition to the extensive population-based epidemiological studies described above, a growing body of evidence gathered from laboratory and clinical settings using human volunteers, is providing further evidence of the addictive effects of nicotine.

Pharmacology. 1984;83:49-55.

Goldberg, note 35, *supra,* at pp. 573-575.

Slifer BL, Balster RL. Intravenous self-administration of nicotine: with and without schedule-induction. *Pharmacol. Biochem. Behav.* 1985;22:61-69.

Corrigall WA, Franklin KBJ, Coen KM, Clarke PBS. The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. *Psychopharmacology*. 1992;107:285-289.

[94] *See*:
Goldberg, note 35, *supra,* at pp. 573-575.

Henningfield, note 35, *supra,* at pp. 989-992.

(i) Evaluation of Subjective Effects

In one study, smokers with histories of abuse of other drugs identified intravenous or inhaled nicotine as being a euphoriant similar to cocaine or amphetamine.[95] Using a common measure of the subjective effects of addictive drugs (the Addiction Research Center Inventory), nicotine produced a dose-related increase in the "euphoria" scale (also known as the morphine-benzedrine group scale).[96] This study shows that nicotine produces subjective effects that are similar to those of other addictive drugs. (See Appendix 1 for a summary of the studies on the subjective effects of nicotine.)

(ii) Self-Administration Studies

Human self-administration of nicotine has been demonstrated under controlled laboratory conditions. Smokers were provided the opportunity to give themselves injections of nicotine in test sessions where they were not allowed to smoke.[97] The subjects self-administered nicotine in a regular, orderly pattern, giving themselves roughly the same amount of nicotine as they were accustomed to getting from their cigarette smoking.[98] (See Appendix 1 for a summary of the studies establishing that nicotine is a positive reinforcer in

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[95] *See:*
Surgeon General's Report. 1988. *Nicotine Addiction.* Pages 177-178.

Henningfield et al, note 21, *supra.*

[96] *Id.*

[97] Henningfield JE, Miyasato K, Jasinski DR. Cigarette smokers self-administer intravenous nicotine. *Pharm Biochem Behav.* 1983;19:887-890.

[98] *Id.*

human self-administration studies.)

c. Studies on Tolerance and Withdrawal

"Tolerance" is produced by a substance when the effects of the substance, at a given dose, become less intense over time, or when an increasing dose over time is necessary to cause an effect or response of a specified intensity. It is well documented that nicotine produces tolerance in users. For example, novice smokers usually experience nicotine-related effects such as dizziness, nausea, vomiting, and headaches.[99] These effects are not produced in experienced smokers because they rapidly develop a tolerance to nicotine. Eventually, smokers increase the amount that they will smoke, always ensuring that the level of nicotine intake will fall below the level at which they would suffer undesirable physical effects and above the level at which they would begin to experience withdrawal symptoms.[100] Tolerance to nicotine is not complete, because even the heaviest smokers can experience symptoms, such as nausea and vomiting, when they suddenly increase their smoking rates.[101] Additionally, the amount of nicotine needed to maintain an addiction may plateau. (See Appendix 1 for a summary of studies demonstrating tolerance to nicotine.)

Clinical studies on nicotine withdrawal have demonstrated that physiological effects

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[99] Surgeon General's Report. 1994. *Preventing Tobacco Use Among Young People*. Page 138.

[100] Rose JE, Behm FM, Levin ED. The role of nicotine dose and sensory cues in the regulation of smoke intake. *Pharm Biochem and Behav.* 1993;44:891-900.

[101] *See:*
Danaher BG. Research on rapid smoking: Interim summary and recommendations. *Addictive Behaviors.* 1977;2:151-166.

Surgeon General's Report. 1988. *Nicotine Addiction*. Page 50.

occur as a result of tobacco deprivation. These effects include decreased heart rate, decreased arousal evidenced by diminished alertness, central nervous system changes, decreases in blood pressure, and disruptions in sleep patterns.[102] Studies have also demonstrated that tobacco withdrawal can cause an increase in weight. This weight increase may be attributed to increased caloric intake, decreased metabolism, and decreased energy expenditure following nicotine withdrawal.[103]

After several weeks of nicotine exposure, users who are deprived of nicotine for more than a few hours develop withdrawal symptoms. The most common self-reported withdrawal symptoms in nicotine-deprived smokers and smokeless tobacco users are increased irritability, anxiety, difficulty concentrating, restlessness, impatience, and insomnia.[104] Withdrawal symptoms after quitting tobacco use can persist for months.[105] Although nicotine withdrawal is not as severe as withdrawal from heroin or alcohol, it is comparable to withdrawal from other stimulants such as cocaine, and can be highly disruptive to personal

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[102] *See:*
West RJ, Jarvis MJ, Russell MAH, Caruthers ME, Feyerabend C. Effect of nicotine replacement on the cigarette withdrawal syndrome. *British Journal of Addiction.* 1984;79(2):215-219.

Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatry.* 1986;43:289-294.

[103] *See:*
Wack JT, Rodin J. Smoking and its effect on body weight and the systems of caloric regulation. *The American Journal of Clinical Nutrition.* 1982;35(2):366-380.

Glauser SC, Glauser EM, Reidenberg MM, Reisy BF, Tallarida RJ. Metabolic changes associated with the cessation of cigarette smoking. *Archives of Environmental Health.* 1970;20:377-381.

[104] *See* Hughes, note 102, *supra,* at pp. 289-294.

[105] Ryan FJ. Cold Turkey in Greenfield, Iowa: A Follow-up Study. In: Dunn WL, ed. *Smoking Behavior: Motives and Incentives.* Washington, DC: VH Winston & Sons; 1973:231-234.

life.[106]

[106] Benowitz NL. Cigarette smoking and nicotine addiction. *Medical Clinics of N. America.* 1992;76(2):415-437.

4. Nicotine's Sensory Effects Are Secondary to its Psychoactive Effects

Nicotine is an irritant to the throat and upper respiratory system.[107] Its effects in the throat contribute to the harshness of tobacco smoke reported by smokers.[108] Many beginning smokers report that the taste of cigarettes is unpleasant.[109] Despite these facts, those who continue to smoke report that they enjoy the taste of commercial tobacco products.[110] In some studies, low-nicotine or nicotine-free products that replicate the taste, flavor, or throat and chest sensations of cigarette smoking can, in the very short term, reduce certain nicotine withdrawal symptoms, including craving for cigarettes.[111] Significantly, however, many of the positively perceived aspects of the harsh taste and flavor of commercial tobacco products are due to "secondary reinforcement." This is a phenomenon by which smokers associate the irritant effects of nicotine in the mouth and throat with desired psychoactive effects that occur immediately thereafter.[112] These irritant effects are then judged favorably, because they are

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[107] *See* Rose, note 100, *supra.*

[108] Rose JE, Sampson A, Levin ED, Henningfield JE. Mecamylamine Increases Nicotine Preference and Attenuates Nicotine Discrimination. *Pharm Biochem and Behav.* 1989;32:933-938.

[109] Surgeon General's Report. 1994. *Preventing Tobacco Use Among Young People.* Page 138.

[110] *Id.*

[111] *See:*
Rose JE, Behm F. Refined cigarette smoke as a method for reducing nicotine intake. *Pharmacology Biochemistry and Behavior.* 1987;28:305-310.

Levin ED, Rose JE, Behm F. Development of a citric acid aerosol as a smoking cessation aid. *Drug and Alcohol Dependence.* 1990;25:273-279.

Rose JE, Behm FM. Inhalation of vapor from black pepper extract reduces smoking withdrawal symptoms. *Drug and Alcohol Dependence.* 1994;34:225-229.

[112] *See:*
Rose, note 100, *supra.*

associated with the delivery of the psychoactive properties of nicotine. The conditioning process is similar to that which occurs for other dependence-producing drugs in which effects that are disliked upon initial exposure come to be associated with desired psychoactive effects.[113] Experienced smokers can use the irritant effects of nicotine to assess how much nicotine they are delivering to themselves while they are smoking.[114]

Data indicate that long-term smoking is continued not because of the taste characteristics of tobacco but because of other factors, specifically the pharmacological effects of nicotine.[115] Evidence gathered from nicotine replacement products supports this position. As noted, two nicotine dosage forms are on the market for treatment of nicotine withdrawal as an aid to smoking cessation (nicotine polacrilex gum and nicotine transdermal patches). FDA is reviewing a New Drug Application (NDA) for a third dosage form, an aqueous nicotine nasal spray. The nicotine nasal spray was the subject of an August 1994 FDA Drug Abuse Advisory Committee meeting because of its possible addiction liability. Among subjects who used the spray for a year during one of the trials, several reported that they felt dependent on the spray, displayed withdrawal symptoms upon stopping the spray,

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Levin ED, Behm F, Rose JE. The use of flavor in cigarette substitutes. *Drug and Alcohol Dependence.* 1990;26:115-160.

Rose JE, Tashkin DP, Ertle A, Zinser MC, Lafer R. Sensory blockade of smoking satisfaction. *Pharmacology Biochemistry and Behavior.* 1985;23:289-293.

[113] Surgeon General's Report. 1988. Nicotine Addiction. Pages 264-265, 309.

[114] *See* Rose, note 100, *supra.*

[115] *See:*
Rose, Tashkin, et al, note 112, *supra.*

Rose, note 100, *supra.*

and sometimes used the spray in larger quantities and more frequently than was required by the study protocol -- all despite the fact that use of the spray was unpleasant and caused nasal ulcers and other medical problems for some participants.[116]

The ability of nicotine nasal spray to produce some of the classic characteristics of addiction to nicotine supports the position that tobacco users seek nicotine primarily for its systemic pharmacological effects, and not for its acute sensory effects. The spray vehicle and dispensing system of the nicotine nasal spray are rudimentary; it is merely nicotine in water forced through an aspirator to make a nasal mist. In contrast to cigarette smoke, aqueous nicotine spray does not provide the user any pleasing sensory characteristics. In fact, the spray can be irritating and unpleasant to use, can impart a very unpleasant taste if it runs down the nose and into the throat, and excessive use can cause ulcerations of the nasal mucosa. Notwithstanding the unpleasantness of the nicotine delivery mechanism, and the presence of painful ulcerations that were further aggravated by continued use of the spray, the spray was used to maintain nicotine dependence for many of the participants in its clinical trials.[117]

The dependence upon nicotine nasal spray illustrates a physical need for nicotine's pharmacological effects, not merely in the absence of any pleasurable sensory effects that may be associated with nicotine in cigarette smoke, but even in the face of rather unpleasant

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[116] E. Douglas Kramer, M.D. Testimony before the Drug Abuse Advisory Committee. August 1, 1994. Drug Abuse Advisory Committee Meeting Transcript. Pages 58-63. Nicotine nasal spray is unique among nicotine replacement therapies in that it produces peak blood levels of nicotine almost as quickly as inhalation of cigarette smoke.

[117] FDA Drug Abuse Advisory Committee Background Information. August 1, 1994. Joint Abuse Liability Review of Nicotine Nasal Spray.

and even painful sensations. This provides strong evidence that nicotine is sought by tobacco users who are dependent upon it for reasons other than its pleasurable, acute sensory effects in the mouth, nose, and throat.

5. Other Factors Associated with Tobacco Use Are Secondary

There are other factors that play a role in the decisions to begin and continue the use of tobacco.[118] For example, social and psychological factors play a role in the initiation of smoking and, to a lesser extent, the maintenance of tobacco use.[119] In particular, parents, peers, and older siblings greatly influence the likelihood that a young person will smoke cigarettes.[120] There is also evidence that adolescents begin to smoke because it promotes sociability, plays a part in establishing friendships, and because it makes them feel mature.[121] Tobacco advertising also plays a role in the decision to start using tobacco.[122] It is recognized

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[118] Tate JC, Pomerleau CS, Pomerleau OF. Pharmacological and non-pharmacological smoking motives: a replication and extension. *Addiction.* 1994;89:322.

[119] *See:*
Surgeon General's Report. 1994. *Preventing Tobacco Use Among Young People.* Pages 124-140.

Stepney R. Smoking behaviour: A psychology of the cigarette habit. *Br J Dis Chest.* 1980;74:325-344.

[120] *See:*
Bewley BR, Bland JM, Harris R. Factors associated with the starting of cigarette smoking by primary school children. *Brit J Prev Soc Med.* 1974;28:37-44.

Murray M, Cracknell A. Adolescents' views on smoking. *J Psychosom Res.*1980;24:248-249.

Banks MH, Bewley BR, Bland JM, Dean JR, Pollard V. Long-term study of smoking by secondary schoolchildren. *Arch Disease in Childhood.* 1978;53:14-16.

[121] *See:*
Bewley, note 120, *supra.*

Bewley BR, Bland JM. Academic performance and social factors related to cigarette smoking by schoolchildren. *Brit J Prev Soc Med.* 1977;31:18-24.

Surgeon General's Report. 1994. *Preventing Tobacco Use Among Young People.* Page 124.

[122] *See:*
Surgeon General's Report. 1994. *Preventing Tobacco Use Among Young People.* Pages 191-192.

Cocores JA. Smokeless Tobacco. In: Cocores JA, ed. *The Clinical Management of Nicotine Dependence.* New York, NY: Springer-Verlag; 1991:49.

that many of the mannerisms and processes associated with smoking may, in the perception of the smoker, become pleasurably linked with tobacco use. These mannerisms or processes may deliver some element of pleasure to the smoker, independent of the inhalation of tobacco smoke.[123]

It is widely accepted, however, by medical and public health groups that the maintenance of tobacco use is due primarily to the addictive properties of nicotine and not solely to these social and psychological factors.

[123] Christen AG, Glover ED. Psychological satisfactions derived from smoking cigarettes in fifty-seven dental patients. *J Drug Educ.* 1983;13(1):95-102.

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

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[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]

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[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

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[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

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[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]

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[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

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[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.

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

Benowitz, note 134, *supra.*

Gori et al, note 142, *supra.*

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

D. CONSUMERS USE TOBACCO PRODUCTS FOR DRUG EFFECTS

1. To Satisfy Addiction

Nicotine, at levels present in commercially marketed tobacco products, is addictive to most users. Most people who use tobacco products do so to maintain their addiction.

A number of studies have been conducted to determine the prevalence of tobacco or nicotine dependence among smokers according to accepted definitions of dependence. Major recent studies conclude that at least 75% and as many as 90% of frequent smokers meet the criteria for addiction established by major public health organizations.[145]

In a 1987 paper by Hughes et al.[146] the authors reported on their efforts to determine the prevalence of tobacco dependence using several diagnostic measures. The study participants included 1,006 middle-aged men in the Minneapolis-St. Paul metropolitan area.[147] The mean number of cigarettes smoked per day in this sample was 28, and the mean number of years smoked was 33. Forty-two percent (n=423) of the subjects had made at least three prior attempts at quitting; 61% (n=614) had made at least one unsuccessful attempt to stop

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[145] Hughes JR, Gust SW, Pechacek TF. Prevalence of tobacco dependence and withdrawal. *Am J Psychiatry*. 1987;144(2):205-208. The precise number of tobacco users found to meet the criteria for nicotine dependence varies depending on the population studied and the study methods used. *See* Appendix 1.

[146] *Id.*

[147] Although utilizing a sample of men only may raise questions about the generalizability of these findings, as the authors point out, previous studies have found that age and sex have little or no effect on tobacco dependence and withdrawal. *See:*

Shiffman SM. The tobacco withdrawal syndrome. In: Krasnegor NA, ed. *Cigarette Smoking as a Dependence Process*. NIDA Research Monograph 23. DHEW Publication No. ADM 79-800. Washington, DC: U.S. Government Printing Office. 1979.

Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatry* 1986;43:289-294.

smoking. The investigators concluded that 90% (n=905) of the smokers fulfilled the DSM-III criteria for tobacco dependence.

Hale et al. surveyed 201 residents of Burlington, VT. Using the DSM-III-R criteria for drug dependence, the researchers concluded that 80% of the current tobacco users were dependent (Male=91%, Female=71%). The most commonly met criteria were unsuccessful attempts to control use despite a persistent desire to quit (93%) and experiencing withdrawal symptoms when stopping or cutting down (74%).[148]

In another study, Cottler compared the various DSM and ICD diagnostic criteria for nicotine dependence among persons who reported smoking or using tobacco daily for 1 month or more during their lives. Sixty-three percent of the sample included patients from substance abuse treatment programs; 37% of the sample was drawn from the general population. Among the 677 nicotine users who fulfilled the smoking or tobacco use requirement, 77% were deemed dependent under the DSM-III diagnostic criteria. Eighty percent met the criteria for dependence according to the DSM-III-R criteria. Under the old ICD-10 criteria, 92% were found to be dependent, compared with 86% under the new ICD-10 criteria.[149]

Woody et al. analyzed the responses of 1,100 subjects who had identified themselves as having used tobacco six or more times during their lives. Subjects were all between 18 and

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[148] Hale KL, Hughes JR, Oliveto AH, et al. Nicotine dependence in a population-based sample: problems of drug dependence, 1992. Proceedings of the 54th Annual Scientific Meeting of the College on Problems of Drug Dependence. NIDA Research Monograph 132. NIH Publication No. 93-3505. Washington, DC. U.S. Government Printing Office. 1993.

[149] Cottler LB. Comparing DSM-III-R and ICD-10 substance use disorders. *Addiction.* 1993;88:689-696.

44 years of age. The researchers found that 87% of those who used tobacco six or more times were dependent under the DSM-III-R criteria.[150] These studies show that a consistently high percentage of smokers are dependent on nicotine, despite the different measuring tools used to evaluate dependence.

As described on p. 90 et seq., studies have also shown that a significant proportion of smokeless tobacco users are addicted.

[150] Woody GE, Cottler LB, Cacciola J. Severity of dependence: data from the DSM-IV field trials. *Addiction.* 1993;88:1573-1579.

2. To Affect Mood and Control Weight

a. Mood

Surveys show that people use tobacco to achieve a relaxing effect, both in stressful situations and to enhance pleasure.[151] For example, one survey found that 65% to 75% of adults believed that smoking reduced nervous irritation.[152] Similarly, a recent survey of young people aged 10 to 22 found that of daily smokers, 72.8% said that smoking relaxed them. Of daily smokeless tobacco users, 53.8% reported that smokeless tobacco relaxed them.[153] Studies also have shown that smokers use cigarettes in an attempt to reduce negative feelings.[154]

The 1988 Surgeon General Report reviewed the epidemiological literature on the effects of smoking on mood and concluded:

> *The conclusion from this literature is that in the general population, persons perceive that smoking has functions that are relevant for mood regulation. Persons report that they smoke more in situations involving negative mood, and they perceive that smoking helps them to feel better in such situations . . . .These data do not necessarily indicate that the various functions characterize different types of smokers; rather, they suggest that most functions are salient to an individual but are operative at different times or in*

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[151] Surgeon General's Report. 1988. *Nicotine Addiction.* Pages 394-399.

[152] *See:*
McKennell AC. Smoking motivation factors. *Br J of Soc and Clin Psych.* 1970;49(1):8-22.

Surgeon General's Report. 1988. *Nicotine Addiction.* Page 399.

[153] *See* CDC, note 86, *supra.*

[154] *See:*
Horn D. Some factors in smoking and its cessation. In: Borgatta EF, Evans RR, eds. *Smoking Health and Behavior.* Chicago, IL: Aldine Publishing Co.; 1968:12-21.

Ikard FF, Green DE, Horn D. A scale to differentiate between types of smoking as related to the management of affect. *Int J Addict.* 1969;4(4):649-59.

different situations."[155]

b. Weight Control

Numerous studies show that smokers believe that smoking keeps weight down and that weight control is a significant motivation to continue smoking.[156] In two surveys of young people, between a third and one-half of smokers offered weight control as a reason for smoking.[157] It has also been suggested that weight gain that occurs after smoking cessation causes many smokers to relapse to smoking.[158]

Research indicates that smoking may play a role in regulating weight. The 1988 Surgeon General's Report summarized the available data:

> *In summary, there is substantial evidence of an inverse relationship between cigarette smoking and body weight. Of 71 studies reported since 1970, 62 (87%) collectively indicate that smokers weigh less than nonsmokers and that people who quit smoking gain weight.*[159]
>
> *Animal studies indicate that nicotine administration results in weight loss or decreased weight gains and that cessation of nicotine results in body weight gains greater than those of controls [animals who did not receive nicotine].*

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[155] Surgeon General's Report. 1988. *Nicotine Addiction.* Page 399.

[156] *See:*

Pomerleau CS, Ehrlich E, Tate JC, Marks JL, Flessland KA, Pomerleau OF. The female weight-control smoker: a profile. *J Substance Abuse.* 1993;5:391-400.

Feldman W, Hodgson C, Corber S. Relationship between higher prevalence of smoking and weight concern amongst adolescent girls. *Canadian Journal of Public Health.* 1985;76(3):205-206.

Surgeon General's Report. 1988. *Nicotine Addiction.* Pages 414-432.

[157] Surgeon General's Report. 1988. *Nicotine Addiction.* Page 438.

[158] *Id.* at pp. 414, 438-441.

[159] *Id.* at p. 431.

Recent research on nicotine polacrilex gum with humans corroborates the role of nicotine in body weight effects.[160]

It is clear from the evidence that consumers use tobacco products for several well-defined and well-documented drug effects. Most significantly, consumers use tobacco products to maintain their addiction to nicotine. Consumers also use tobacco for a variety of ancillary drug effects. These include the effects of nicotine on mood and weight control.

[160] *Id.* at p. 432.

II. STATEMENTS, RESEARCH, AND ACTIONS BY TOBACCO COMPANIES

The evidence presented in this section describes the statements, research activities, and actions of the tobacco industry related to the role of nicotine in cigarettes and smokeless tobacco. Industry statements show that tobacco company officials at the highest levels are aware that nicotine's drug effects are the primary reason people use their products. The tobacco industry's research shows that it has knowledge of the pharmacological role of nicotine in tobacco use, including its ability to affect brain function and behavior and to produce dependence. The industry has also conducted research to determine what constitutes an adequate dose of nicotine. The tobacco industry's actions show that it has manipulated nicotine delivery in marketed products and attempted to develop products to provide a dose of nicotine that satisfies consumers' desire for the pharmacological effects of nicotine.

A. INDUSTRY STATEMENTS ON NICOTINE'S DRUG EFFECTS

Recently disclosed industry documents contain explicit statements, made by high-ranking tobacco company officials over more than three decades, acknowledging nicotine's drug effects and the central role those effects play in tobacco use. These documents also include research reports and conference summaries describing the specific pharmacological and physiological effects of nicotine, including, in some cases, its addictive properties. Covering a period of more than 30 years, these company documents show that tobacco companies have long recognized that nicotine in tobacco is a drug, that nicotine is the primary reason people use cigarettes and smokeless tobacco, and that cigarettes and smokeless tobacco are nicotine delivery systems. Internal statements of company officials and researchers reflect the industry's true knowledge and real intentions. The internal statements contained in these documents confirm that tobacco manufacturers intend nicotine-containing cigarettes and smokeless tobacco to be used as drugs. The extent of these statements was not known to FDA at the time of its earlier determinations about the intended use of tobacco.

1. Statements That Nicotine's Drug Effects Are Essential to Tobacco Use

Tobacco company researchers have, for more than 30 years, studied the effects of nicotine on the body. Industry documents reveal that the manufacturers' research has convinced the industry that nicotine in tobacco produces pharmacological effects in tobacco users and that these effects are the major reason that consumers use tobacco products. These documents reveal further that tobacco company executives and senior officials share these convictions about the central role of nicotine's drug effects in tobacco use.

a. Tobacco Company Researchers' Views

A wide range of industry documents reveals that tobacco company researchers have known for several decades that nicotine in tobacco functions as a drug and that nicotine's drug effects are the central reason that consumers use tobacco.

More than 30 years ago, in 1962-63, BATCO received the results of its Project HIPPO study (HIPPO I and HIPPO II), the aim of which was to "understand some of the activities of nicotine -- those activities that could explain why smokers are so fond of their habit."[161] A second purpose of the Project HIPPO study was to compare the effects of nicotine with those of then-new tranquilizers, "which might supersede tobacco habits in the near future."[162] Thus,

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[161] *See:*

Hersch J, Libert O, Rogg-Effront C. *Final Report on Project HIPPO I.* Battelle Memorial Institute. International Division. Geneva, Switzerland. January 1962. (Hereafter cited as Final Report on Project HIPPO I.)

Haselbach CH, Libert O. *Final Report on Project HIPPO II.* Battelle Memorial Institute. International Division. Geneva, Switzerland. March 1963. Pages 1-3. (Hereafter cited as Final Report on Project HIPPO II.)

[162] *Id.* Final Report on Project HIPPO II. Page 1.

these researchers believed that nicotine-containing tobacco and tranquilizers were used for the same purposes by consumers. The researchers concluded that, despite some similarities, nicotine has different drug effects than tranquilizers:

> *both kinds of drugs [nicotine and tranquilizers] act quite differently, and [] nicotine may be considered (its cardiovascular effects not being contemplated here) as more "beneficial" or less noxious -- than the new tranquilizers from some very important points of view.*
>
> *The so-called "beneficial" effects of nicotine are of two kinds:*
> *1. Enhancing effect on the pituitary adrenal response to stress;*
> *2. Regulation of body weight.*[163] [Emphasis added.]

In the final conclusion of the HIPPO study, the researchers discuss the effect of nicotine in the "stress reaction":

> *The understanding and thorough investigation of this effect seems of the greatest importance: it is by this very effect that nicotine acts as a 'tranquilliser.'*[164]

The Project HIPPO reports were disseminated to officials of Brown and Williamson (B&W).[165] The exchange of information between BATCO and B&W is important because it

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[163] Final Report on Project Hippo II. Page 2. Based on studies of rats, the Project HIPPO I researchers also concluded:

> *We have been in a position to show a definite enhancing effect of nicotine in the normal mechanism of defence [sic] against stress, i.e., in the stimulation of the release of the pituitary corticotropic hormone (ACTH).*

Final Report on Project HIPPO I. Page 2.

[164] Final Report on Project HIPPO I. Page 48.

[165] These reports were also circulated to various other U.S. tobacco companies, and the Tobacco Industry Research Committee, the forerunner to the Council for Tobacco Research (Little, CC. "Report of the Scientific Director," 1963, at p. 5), demonstrating that at least some of the industry's nicotine research was shared. *See, e.g.*:

June 28, 1963, letter from Sir Charles Ellis, Scientific Advisor to the Board of BATCO to A. Yeaman of B&W.

August 5, 1963, letter from A. Yeaman to E.J. Jacob of R.J. Reynolds Tobacco Co.:

demonstrates B&W's awareness of the results of studies such as Project HIPPO,[166] which was just one of a number of studies commissioned by BATCO to study the physiological and pharmacological effects of nicotine. For example, a 1980 report addresses the critical role of nicotine's drug effects:

> *Nicotine is an extremely biologically active compound capable of eliciting a range of pharmacological, biochemical, and physiological responses in vivo . . . In some instances, the pharmacological response of smokers to nicotine is believed to be responsible for an individual's smoking behaviour, providing the motivation for and the degree of satisfaction required by the smoker.*[167]

The BATCO documents include not only some of the research reports themselves, bu also summaries or minutes of numerous BATCO research and development (R&D) meetings at which nicotine's drug effects and importance to the industry were discussed. These papers demonstrate both the consistency and the extent of industry's interest in and knowledge of

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I suggest to you and Henry that it is now timely to release these reports to the S.A.B. [Scientific Advisory Board of the Tobacco Institute Research Council].

June 19, 1963, note for Mr. Cutchins of B&W, noting that Sir Charles Ellis had sent Mr. Cutchins reports of research that BATCO had sponsored at Battelle :

> . . . . *showing the beneficial effects of nicotine . . . . BAT decided to make this research available to the T.R.C. [Tobacco Research Council of the U.K.] . . . .Todd, of T.R.C. is to-day sending copies to T.I.R.C. [Tobacco Industry Research Committee of the U.S.] with a request that they consider whether it would help the U.S. industry for these reports to be passed on to the Surgeon General's Committee.*

[166] Appendix 2 contains a detailed description of how the research was shared between B&W and BATCO. The B&W/BATCO documents that recently were made public offer an extraordinary glimpse into the workings of the third largest U.S. tobacco company. Although the five other leading U.S. tobacco companies received requests from FDA on July 11, 1994, for similar documentary evidence, to date the companies have failed to provide the requested information. *See* Appendix 3. Tobacco industry material is cited throughout the Legal Analysis and Findings sections of this document that refers to the workings of the five U.S. tobacco companies. This material constitutes just a representative sample of the internal information still in the possession of those companies.

[167] BATCO Group R &.D. Southampton, England. *Method for Nicotine and Cotinine in Blood and Urine.* Report No. RD.1737-C. May 21, 1980. Page 2.

nicotine as the primary pharmacological agent in tobacco. For example, at a 1974 BATCO Group R&D Meeting, it was noted that:

> *Nicotine (which has been assumed to be the main pharmacologically active component in smoke) may act in a bi-phasic manner, either as a stimulant (CNV increase) or depressant (CNV decrease).*[168]

In addition, a 1977 report concerning an International Smoking Behavior Conference includes the following statements about nicotine's effects:

> *Nicotine was the focal point of the conference. In many cases, psychological and physiological changes observed in subjects . . . . were shown to be due to nicotine.*
>
> *Most researchers conclude that the nicotine effect is biphasic and dosage dependent; small doses stimulate and large doses depress.*[169]

Subsequent BATCO research conferences offer equally revealing statements about the drug effects of nicotine. A BATCO Group R&D Smoking Behaviour-Marketing Conference held in 1984 focused almost entirely on the role of nicotine pharmacology in smoking. Summaries of the presentations at that conference include numerous references to the pharmacological effects of nicotine and the importance of these effects in maintaining tobacco use. For example, one presentation included the following observation:

> *Smoking is then seen as a personal tool used by the smoker to refine his behaviour and reactions to the world at large.*
>
> *It is apparent that nicotine largely underpins these contributions through its role as a generator of central physiological arousal effects which express*

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[168] BATCO Group R&D. Southampton, England. *Interaction of Smoke and the Smoker, Part 3: The Effect of Cigarette Smoking on the Contingent Negative Variation.* Report No. RD.1164-R. December 12, 1974. Page 1.

[169] BATCO International Smoking Behavior Conference: Trip Report. Chelwood Vachery, England. November 27-30, 1977. Pages 1-2.

> *themselves as changes in human performance and psychological well-being.*[170] [Emphasis added.]

Reporting on a study testing the hypothesis that extroverts smoke for nicotine and introverts smoke for the motor activity provided by smoking, another presentation concluded:

> *Extraverts [sic] relied principally on nicotine and did not pay attention to the motor aspects of smoking except to gain nicotine and so did not show well developed motor potentials preceding the motor act. However, the effect of nicotine is to enhance the extravert's motivation to act, and this increases motor activity rate after smoking (as was shown in the tapping rate recorded for extraverts after smoking) . . . . For preparatory smokers (extraverts): Smoking functions as a kind of portable, stationary generator inducing the effects of activity on the CNS [central nervous system] without the usual requirement of stressful activity to achieve those effects.*[171]

Finally, another BATCO conference focusing on nicotine was held in 1984. One of the presentations was characterized by a Brown and Williamson official:

> *The presentation was concerned with summarising and outlining the central role of nicotine in the smoking process and our business generally. . . There are two areas of nicotine action that are of primary importance: (i.) to identify to what extent the pharmacological properties or responses to nicotine are influenced by blood and tissue levels of nicotine. (ii) what is the significance and role of nicotine in eliciting the impact response and upper respiratory tract responses . . .* [Emphasis added.][172]

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[170] Ferris RP. *The role of smoking behavior in product development: some observations on the psychological aspects of smoking behaviour.* In: Proceedings of the BATCO Smoking Behaviour-Marketing Conference, Session III. July 9-12, 1984. Page 79.

[171] Proceedings of the BATCO Smoking Behaviour-Marketing Conference, Session III. July 9-12, 1984. Slides. Pages BW-W2-02772-02775.

[172] Ayres CI. Notes from the GR&DC [Group Research and Development Centre] Nicotine Conference June, 1984. Page 62. The conference was devoted predominantly to nicotine's pharmacological effects. The conference's seven sessions are listed as follows:

> *Session I - Nicotine Dose Requirement - Background; Session II - Nicotine Dose Estimation; Session III - Sensory and Psychological Effects of Nicotine; Session IV - Effect of Nicotine - Interaction with the Brain (Pharmacology); Session V - Effects of Nicotine - Interaction with Peripheral Tissues (Physiology);Session VI - Product Modification for Maximal Nicotine Effects Session VII - General Session.* Pages BW-W2-02639, 12641-46.

See also:

As described in FINDINGS § II.B., infra, comparable research on the pharmacological effects of nicotine has been conducted or sponsored by all the major tobacco companies. For example, researchers at the R.J. Reynolds Tobacco Co. have published studies in which they freely acknowledge the pharmacological effects of nicotine in tobacco and the importance of those effects to smokers:

> *The beneficial effects of smoking on cognitive performance . . . are a function of nicotine absorbed from cigarette smoke upon inhalation.*[173]

BATCO R&D Conference. Hilton Head, SC. September 24-30, 1968. Page 3. The conferees recognized "that the reasons why people smoke are partly pharmacological and partly psychological."

BATCO R&D Conference. Montreal, Canada. October 25, 1967. Page 6. The conferees concluded: *While recognizing the importance of psychological factors in smoking and the possibility that some smokers would accept non-nicotine cigarettes, it was felt that nicotine is important for the majority of smokers and that the form of nicotine can be significant.* [Emphasis added.]

BATCO R&D Conference. Kronberg, Germany. June 2-6, 1969. Page 7 of summary: *The Conference agreed that all the evidence continues to demonstrate the importance of nicotine to the smoker, and again emphasises the importance of keeping separate TPM and nicotine figures.* [Emphasis added.]

BATCO Group R&D report. Southampton, England. *Preparation and Properties of Nicotine Analogues.* Report No. RD 953-R. November 9, 1972.

BATCO Group R&D Conference on Smoking Behavior. Southampton, England. October 11-12, 1976. Pages BW-W2-02145-02149, BW-W2-02150-02165, BW-W2-02292-02311.

February 9, 1984, letter from C.I. Ayres to E.E. Kohnhorst (both of Brown and Williamson) summarizing the August 30-September 3, 1982, BATCO R&D Conference. Montebello, Canada.

[173] Robinson JH, Pritchard WS, Davis RA (R.J. Reynolds Tobacco Co.). Psychopharmacological effects of smoking a cigarette with typical "tar" and carbon monoxide yields but minimal nicotine. *Psychopharmacology.* 1992;108:471.

See also Pritchard WS, Robinson JH, Guy TD (R.J. Reynolds Tobacco Co.). Enhancement of continuous performance task reaction time by smoking in non-deprived smokers. *Psychopharmacology.* 1992;108:437-442.

Pritchard WS, Gilbert DG, Duke DW (R.J. Reynolds Tobacco Co.). Flexible effects of quantified cigarette smoke delivery on EEG dimensional complexity. *Psychopharmacology.* 1993;113:95-102.

> *An enduring question regarding human cigarette smoking is the basis of the so-called "nicotine paradox." Although the peripheral effects of smoking appear to be stimulatory (e.g., increased heart rate, especially for the initial cigarette of the day [citation omitted]) and many smokers say that smoking increases their mental alertness, other smokers report that smoking helps them to function in the face of environmental stress by having a calming effect on their mood [citation omitted].*[174]
>
> *We recognize that nicotine plays an important role in smoking behavior for many people.*[175] [Emphasis added.]

Philip Morris researchers conducted extensive research on nicotine pharmacology from the late 1960's until at least the mid-1980's. See note 240a, infra. The nature and magnitude of the research, as well as statements made in internal documents, show that the Philip Morris researchers strongly believed that nicotine has potent psychoactive effects and that these effects provide a primary motivation for smoking. For example, in 1969, a Philip Morris researcher proposed a study whose purpose was to show that cigarette smoking is more likely in stressful situations. The researcher stated that such a study would demonstrate "one of the advantages of smoking, its use as an anxiety reducer."[175a] In 1974, Philip Morris researchers began a study designed to test their theory that hyperkinetic children take up

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[174] Pritchard WS (R.J. Reynolds Tobacco Co.). Electroencephalographic effects of cigarette smoking. *Psychopharmacology.* 1991;104:485-490. Page 00033640. (Smokers who inhale lightly appear to use tobacco to achieve "mental activation and performance enhancement" while those who inhale more deeply achieve effects in the portion of their brains that is associated with anxiety reduction after administration of benzodiazepines. *Id.* at p. 00033643. [Benzodiazepines are drugs used as sedatives and to treat anxiety.])

See also Gibert DG, Robinson JH, Chamberlin CL (R.J. Reynolds Tobacco Co.), and Spielberger, CD. Effects of smoking/nicotine on anxiety, heart rate, and lateralization of EEG during a stressful movie. *Psychophysiology.* 1989;26(3):311-319. (High-nicotine cigarettes associated with reductions in anxiety and activation of the right hemisphere of the brain.)

[175] Robinson J, Pritchard W. The role of nicotine in tobacco use. *Psychopharmacology.* 1992;108:405.

[175a] Memorandum to W.L. Dunn from F.J. Ryan. Proposed Research Project: Smoking and Anxiety. December 23, 1969. *In* 141 Cong. Rec. H7648 (daily ed. July 25, 1995).

smoking in adolescence because nicotine may perform the same pharmacological function as prescription medications used to treat hyperkinesis:

> *It has been found that amphetamines, which are strong stimulants, have the anomalous effect of quieting these children down . . . Many children are therefore regularly administered amphetamines throughout grade school years . . . . We wonder whether such children may not eventually become cigarette smokers in their teenage years as they discover the advantage of self-stimulation via nicotine. We have already collaborated with a local school system in identifying some such children in the third grade.*[175b] [Emphasis added.]

In 1976, a Philip Morris researcher wrote a memo explaining why people smoke. In his memo, he reported on a survey in which smokers were asked why they smoked. The researcher concluded that

> *the circumstances in which smoking occurs may be generalized as follows:*
> *1. As a narcotic, tranquilizer, or sedative. Smokers regularly use cigarettes a times of stress.*
> *2. At the beginning or ending of a basic activity . . . .*
> *3. Automatic smoking behavior. . .*[175c] [Emphasis added.]

In a research paper funded by the Council for Tobacco Research, U.S.A. (CTR),[176]

[175b] Dunn WL. 1600/Smoker Psychology/May 1-31, 1974 [Monthly Report]. June 10, 1974.
See also:
Memorandum from W.L. Dunn to P.A. Eichorn. Quarterly Report- February-March, 1972. April 4, 1972. This memo reports on a study conducted by Philip Morris comparing the "arousal response" produced by nicotine, caffeine, and placebo. The researchers reported that the "arousal response was clearly present with nicotine" and that the caffeine response was nearer to placebo. *In* 141 Cong. Rec. H7651 (daily ed. July 25, 1995).

[175c] Memorandum from A. Udow, Philip Morris, New York, NY, to Mr. J.J. Morgan. Why People Start to Smoke. June 2, 1976. *In* 141 Cong. Rec. H7664 (daily ed. July 25, 1995).

[176] In January, 1954, 14 presidents of tobacco manufacturers, growers, and warehousemen organized the forerunner organization to CTR, known as the Tobacco Industry Research Committee (TIRC), to sponsor a research program into questions of tobacco use and health. (By-laws of the Tobacco Industry Research Committee, subscribed and adopted on January 1, 1954.) TIRC was founded in response to growing concern by tobacco executives over the appearance of published articles claiming an established relationship between cigarette smoking and lung cancer.

reporting on the "beneficial" pharmacological effects of nicotine in cigarettes, the authors said:

> *Nicotine is recognized as the primary psychoactive compound in cigarette smoke.*[177]

Many other industry documents refer to the central role of nicotine's drug effects for smokers and, therefore, for the industry.[178] Nicotine is repeatedly identified as a primary

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The driving force behind the creation of TIRC was Paul M. Hahn, President of the American Tobacco Company. Other original signers of the TIRC by-laws were Timothy V. Hartnett, President of Brown and Williamson Tobacco Corp., Herbert A. Kent, Chairman of P. Lorillard & Co., O. Parker McComas, President of Philip Morris & Co., E.A. Darr, President of R. J. Reynolds Tobacco Co., J.W. Peterson, President of U.S. Tobacco Co., and Joseph F. Cullman, President of Benson & Hedges. (Minutes of the Meeting of the Presidents of the Leading Tobacco Companies at the Hotel Plaza, December 15, 1953. Page 1.)

By 1963, grants had been made to 140 scientists from $6,250,000 appropriated by TIRC from its member companies. In January, 1964, TIRC changed its name to the Council for Tobacco Research (CTR), its current name. The current members of CTR include Philip Morris, R.J. Reynolds, Brown and Williamson, American Tobacco, Lorillard Corp., and U.S. Tobacco. By 1993, CTR had funded more than $223 million in research. Annual Reports issued by CTR reveal that the organization has provided extensive funding to research on nicotine pharmacology. *See* note 195, *infra.*

[177] Levin ED, Briggs SJ, Christopher NC, Rose JE. Persistence of chronic nicotine-induced cognitive facilitation. *Behavioral and Neural Biology*. 1992;58:152-158.

[178] For example, the American Tobacco Company (ATC) published a document entitled *A Summary of Biological Research on Tobacco Supported in Whole or in Part by the American Tobacco Company* (April 1962). In a chapter entitled "Role of Nicotine in the Cigarette Habit," ATC referred to a 1945 study and stated that "[t]he authors concluded that with some individuals, nicotine becomes a major factor in their cigarette habit." Page 66. (*See* Finnegan JK, Larson PS, Haag B. The role of nicotine in the cigarette habit. *Science*. 1945;102:94.)

See also:

Willey LC, Kellett ND (for Imperial Tobacco Group Ltd.). *Effects of Nicotine on the Central Nervous System*. Huntingdon Research Centre. 1971. Page 9:

> *We aim, by using various different schedules of behavioural training, and by comparing the effects of many different drugs on these schedules, to be able to classify the effect of nicotine, when given intermittently in smoking doses, as similar to a known class of drug acting on the central nervous system. Alternatively, it may, perhaps, act like one type of drug in some tests and at some doses and like another type in other tests.*

U.S. Patent No. 4,340,072. Bolt AJ, Chard B. *Smokable Device.* Imperial Group Ltd. 1982. C1:

> *Among the reasons why most people smoke conventional cigarettes is that they wish to*

reason consumers smoke or use other nicotine-containing products. A "Proposal for Low Delivery Project for B&W" prepared by a marketing firm hired by B&W in the late 1970's contained the following statement that a sufficient dose of nicotine is essential to sell cigarettes and, implicitly, to maintain market share based on nicotine addiction:

> *Current market trends clearly indicate a major trend toward low-tar brands although current "ultra" low "tar" brands, have had limited success because of their failure to deliver satisfaction/maintain an adequate nicotine level. An ancillary concern relative to nicotine delivery is that if a satisfying, low-nicotine cigarette were to be developed, it could represent an effective means of withdrawal . . . with severe implications for long-term market growth.* [Emphasis added.][179]

Finally, a 1976 BATCO Conference on Smoking Behavior underscores tobacco industry researchers' awareness of the fundamental importance (to the huge majority of smokers) of nicotine's effects on the brain:

> *Some insight into the likely benefits of smoking follows from a consideration of the properties of nicotine, which is considered to be the reinforcing factor in the smoking habit for at least 80% of smokers* . . . [Emphasis added.][180]

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inhale an aerosol containing nicotine.

Note from S.J. Green (BATCO R&D) to Dr. G. Hook (BATCO R&D). June 11, 1974.

[179] Lisher & Company Inc. memo. Proposal for Low Delivery Project for B&W. On the copy of this proposal, lines 3 - 7, beginning with "maintain an adequate nicotine level," are crossed out. The unedited quote makes clear that the term "satisfaction" is a euphemism used by the industry to refer to satisfaction of the desire for nicotine.

[180] BATCO Group R&D Conference on Smoking Behavior. Group Research and Development Centre. Southampton, England. October 11-12, 1976. *"Benefits" of Smoking.* (Pages BW-W2-02152 and 02153). The summary of a presentation at this conference also notes that all types of tobacco usage -- smoking, chewing and snuffing -- allow nicotine to go directly into the blood and to the brain. The speaker observed that nicotine is not ingested, a route that converts nicotine to a pharmacologically inactive metabolite, cotinine, before it can affect the brain. The summary then notes:

> *It would therefore be surprising if nicotine, which is known to be pharmacologically active in the brain (unlike cotinine), and which is obtained in the ways most likely to enable it to reach the brain unchanged, were not involved in the reasons why people smoke.*

Id., Session II: Current Views on the Role of Nicotine in Smoking Behaviour. Page BW-W2-02145.

b. Tobacco company executives' and senior officials' views

Internal and published documents demonstrate that tobacco company executives and senior officials have also long understood that nicotine is a drug and that nicotine's pharmacological effects are essential to consumer satisfaction.

In 1988, during the case Cipollone v. Liggett, Joseph Cullman III, former CEO of the Philip Morris Tobacco Company, testified as follows:

Q: Let me ask you the question, then, Mr. Cullman. Is nicotine a drug?

A: Well it's so described in every book on pharmacology.

Q: So then you agree that it's a drug?

A: I have no reason to disagree with books on pharmacology.[181]

In 1981, the Tobacco Advisory Council, representing the United Kingdom tobacco manufacturers[182] (including BATCO), published a monograph on nicotine pharmacology and toxicology that expressly treats nicotine as a drug delivered by tobacco.[183] The monograph states that "nicotine is regarded as the most pharmacologically-active compound in tobacco smoke" and states that nicotine's main effects, "at doses absorbed by inhalers (i.e. 1 mg approx per cigarette)" are:

> *central stimulation and/or depression (which vary with the individual), transient hyperpnoea, peripheral vasoconstriction (usually associated with a rise in systolic pressure), suppression of appetite, stimulation of peristalsis and, at larger nicotine intakes, nausea of central origin, associated with*

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[181] *Transcript of proceedings in Cipollone v. Liggett Group, Inc.*, at p. 3290 (D.N.J. Feb. 23, 1988). (Civil Action No. 83-2864 (SA)).

[182] 1981 document of the Tobacco Advisory Council (corrections sheet).

[183] Cohen AJ, Roe FJC. *Monograph on the pharmacology and toxicology of nicotine*. Tobacco Advisory Council. Occasional paper 4. 1981. Page 1.

vomiting.[184]

More than three decades ago, in 1961, a presentation by Dr. Helmut Wakeham, a senior Philip Morris research scientist, to the company's Research and Development Committee noted that:

> *Low nicotine doses stimulate, but high doses depress functions . . . It is also recognised that smoking produces pleasurable reactions or tranquility, and that this is due at least in part to nicotine . . . .*[185]

Dr. Wakeham also noted that "nicotine is believed essential to cigarette acceptability,"[186] a view later restated by William Dunn, Jr., another high-ranking Philip Morris official. In summarizing a 1972 conference sponsored by the Council for Tobacco Research, Dr. Dunn reported:

> *Most of the conferees would agree with this proposition: The primary incentive to cigarette smoking is the immediate salutary effect of inhaled smoke upon body function.* [Emphasis added.][187]

After describing "the physiological effect" as "the primary incentive" for smoking, Dr. Dunn continued:

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[184] *Id.* at p.17.

[185] Wakeham H. *Tobacco and Health -- R&D Approach.* In: 3.10 Tobacco Products Liability Reporter (TPLR) 8.129. *See also* Wakeham H. Presentation to R & D Committee at meeting held in New York Office on November 15, 1961.

Later, when Wakeham was a Vice President at Philip Morris, his introduction to a tobacco industry symposium included the following acknowledgment that nicotine produces psychoactive effects: "Tobacco and other psychoactive plants have probably been part and parcel of our cultural baggage for thousands of years..." Wakeham H. *Tobacco Smoke: Its Formation and Composition.* 31st Tobacco Chemists Research Conference. October 5-7, 1977. Greensboro, NC. In: *Recent Advances in Tobacco Science.* 1977;3:iii.

[186] *Id.*, TPLR 8.129.

[187] Dunn, note 133, *supra,* at p. 3.

> *The majority of the conferees would go even further and accept the proposition that nicotine is the active constituent of cigarette smoke. Without nicotine, the argument goes, there would be no smoking. Some strong evidence can be marshalled to support this argument:*
>
> *1) No one has ever become a cigarette smoker by smoking cigarettes without nicotine.*
>
> *2) Most of the physiological responses to inhaled smoke have been shown to be nicotine-related.*
>
> *3) Despite many low nicotine brand entries in the market place, none of them have captured a substantial segment of the market . . .* [Emphasis added.][188]

In 1969, Dr. Wakeham, then Vice President for Research and Development, briefed the Philip Morris Board of Directors on why people smoke. A draft of his remarks, which contains the notation "delivered with only minor changes," includes several unequivocal statements that cigarettes are smoked for the pharmacological effects of nicotine:

> *[T]he psychosocial motive is not enough to explain continued smoking. Some other motive force takes over to make smoking rewarding in its own right. Long after adolescent preoccupation with self-image has subsided, the cigarette will even preempt food in times of scarcity on the smoker's priority list . . . . We are of the conviction . . . that the ultimate explanation for the perpetuated cigarette habit resides in the pharmacological effect of smoke upon the body of the smoker, the effect being most rewarding to the individual under stress.*[188a]

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[188] *Id.* at p. 4.

[188a] Ryan/Dunn Alternate -Third version of Board presentation. Fall, 1969. *In* 141 Cong. Rec. H7648 (daily ed. July 25, 1995).
See also:
Memorandum to P.A. Eichorn from W.L. Dunn. Five-year Objectives and Plans for Project 1600. September 25, 1970. *In* 141 Cong. Rec. H7650, *supra.* This document details Philip Morris' plans to study the "short-term psychological and psychophysiological" effects of smoking "as manifested through changes in autonomic, perceptual, cognitive and central nervous system processes and motor performance." The author goes so far toward presuming the essential role of nicotine as to propose that research be undertaken to answer the question: "Can the smoking habit be sustained in the absence of nicotine?"

Dunn WL. 1600/Smoker Psychology/January 1- January 31, 1973 [Monthly Report]. February 9, 1973. *In* 141 Cong. Rec. H7650, *supra.* This report shows that several studies were underway at Philip Morris

A 1974 annual report on the Behavioral Research program at Philip Morris approved by Thomas Osdene (later Vice President for science and technology) and distributed to Dr. Wakeham, also reflects the view that cigarettes are drugs consumed for pharmacological effects. The report states that a person regulates smoke intake "to achieve his habitual quota of the pharmacological action [of the components of smoke]." [188b]

In the following year, the annual report on the "Behavioral Research" program explicitly acknowledged that nicotine is a stimulant drug. Describing a theory concerning the effect of an individual's CNS arousal level on performance efficiency, the report says that while one way to increase the CNS arousal level is to seek out stimulating situations, another way is to:

> *consume socially approved chemicals which would have a similar effect on the*

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to determine the effects of nicotine on the central nervous system and on performance, including studies on the effects of smoking on: electrical activity in the brain, the "arousal mechanisms of the central nervous system," and "spare mental capacity."

Philip Morris Research Center. Behavioral Research Annual Report (Part II). November 1, 1974. *In* 141 Cong. Rec. H7658, *supra.* The report lists the following "working hypotheses" of Philip Morris researchers:

> *IA. Cigarette smoke improves efficiency in the performance of complex psychological tasks.*
> *1B. Cigarette smoking attenuates, modulates or otherwise influences emotional arousal such as to be gratifying or rewarding to the smoker, thus reinforcing the smoking act.*
> . . . .
> *IIA. Dose-control continues even after the puff of smoke is drawn into the mouth.*

Dunn WL, Ryan FJ, Martin P. Behavioral Research Annual Report. July 18, 1975. *In* 141 Cong. Rec. H7658, *supra.* This report describes a study being undertaken by Philip Morris, entitled "Nicotine as a Modulator of CNS Arousal." The study was to be conducted because the researchers believed that previous studies had provided evidence that nicotine reduces emotional responsiveness:

> *[Previous] observations imply the influence of nicotine upon some control mechanism governing affective responsivity, the net effect upon overt behavior being to reduce the intensity of the emotionally-toned response, or raise the threshold for the elicitation of that response.*

[188b] Philip Morris Research Center. Behavioral Research Annual Report, Part II. Approved by T.S. Osdene. November 1, 1974. *In* 121 Cong. Rec. H7660 (daily ed. July 25, 1995).

body--such as the stimulant drugs caffeine and nicotine.[188c]

Two years later, William Dunn provided a detailed description of the pharmacological effects produced by nicotine that cause smokers to continue smoking:

> *[T]he doses of nicotine inhaled produce definite, mild, and transient neuropsychopharmacological effects which are positively reinforcing and thus promote repetition of smoking. These effects include: (a) modulation of conditioned behavior; (b) mixed depression and facilitation of the neural substrates of reward; (c) transient (in minutes) EEG and behavioral arousal crudely reminiscent of d-amphetamine but pharmacologically quite different; and at the same time (d) skeletal muscle relaxation.*[188d]

Finally, a memorandum from a Philip Morris official in 1980 confirms the company's view that nicotine's pharmacological effects on the central nervous system are critical to the tobacco industry's success:

> *Nicotine is a powerful pharmacological agent with multiple sites of action and*

[188c] Dunn WL, Ryan FJ, Martin P. Behavioral Research Annual Report. July 18, 1975. *In* 141 Cong. Rec. H7655 (daily ed. July 25, 1995). The same report states that the authors have proposed an international industry conference on "the regulatory influence of nicotine upon behavior."

[188d] Memorandum to T.S. Osdene from W.L. Dunn. Rationale for Investigating the Effects of Smoking upon Electroencephalographic Phenomena. December 22, 1976. [Citing Domino EF, in Dunn (ed.). Smoking Behavior: Motives and Incentives. 1973.] *In* 141 Cong. Rec. H7665 (daily ed. July 25, 1995).
See also:
Philip Morris. Research and Development Five Year Plan-1979-1983. September 1978. *In* 141 Cong. Rec. H7668 (daily ed. July 25, 1995):

> *Nicotine may be the physiologically active component of smoke having the greatest consequence to the consumer.*

Memorandum to T.S. Osdene from W.L. Dunn. Plans and Objectives-1980. January 7, 1980. *In* 141 Cong. Rec. H7671 (daily ed. July 25, 1995). The author reports:

> *Cigarette smoking results in EEG changes associated with arousal, while smoke deprivation results in . . . [brain] waves associated with drowsiness . . . . [S]moke appears to have opposite effects on visual and auditory evoked potentials . . .[N]icotine, rather than being a general stimulant, may be exerting a selective influence on brain structures.* [Emphasis added.]

The same document describes a new research program underway at Philip Morris intended to study, among other things, "how . . . cigarette smoking can have psychosocial consequences through its . . . central-nervous-system-mediated effects upon the coping abilities of the smoking social participant." [Emphasis added.] *Id.*

may be the most important component of cigarette smoke. Nicotine and an understanding of its properties are important to the continued well being of our cigarette business since this alkaloid has been cited often as 'the reason for smoking' and theories have been advanced for 'nicotine titration' by the smoker. Nicotine is known to have effects on the central and peripheral nervous system as well as influencing memory, learning, pain perception, response to stress and level of arousal. [Emphasis added.][189]

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[189] Philip Morris Interoffice Correspondence from J.L. Charles to Dr. R.B. Seligman. Nicotine Receptor Program-University of Rochester. March 18, 1980. Other Philip Morris documents contain similar statements. *See, e.g.:*

Wakeham H. *Smoker Psychology Research. Presented to the PM Board of Directors, November 26, 1969.* Page 11:

> *We are of the conviction, in view of the foregoing, that the ultimate explanation for the perpetuated cigaret habit resides in the pharmacological effect of smoke upon the body of the smoker, the effect being most rewarding to the individual under stress.*

Ryan, FJ. Philip Morris Research Center Special Report. *Exit-Brand Cigarettes: A Study of Ex-smokers.* March 1978. Page 2.

> *We think that most smokers can be considered nicotine seekers, for the pharmacological effect of nicotine is one of the rewards that comes from smoking. When the smoker quits, he foregoes his accustomed nicotine. The change is very noticeable, he misses the reward and so he returns to smoking.*

Philip Morris employee (almost certainly W.L. Dunn). *Smoker Psychology Program Review.* Date not specified. Page 5. This paper states the theory that the reinforcing effects of smoking are

> *likely to be found among the chemical compounds being introduced into the bloodstream . . . Without the chemical compound, the cigarette market would collapse, P.M. would collapse, and we'd all lose our jobs and our consulting fees.*

The same paper later says that the research program at Philip Morris is based on "*a strong conviction about the central role of the pharmacologic effects of inhaled smoke.*" Page 8.

Ryan, FJ, Jones, BW, Martin, PG, Dunn, WL. Behavioral Research Annual Report. July 18, 1975. Pages 18-22, 25.

Memo to H. Wakeham from W.L. Dunn. *Stating the Risk Study Problem.* July 29, 1969. (Tobacco is used by consumers to modulate arousal level, and to avoid withdrawal.)

Memo to W.L. Dunn from T.R. Schori. *Smoking and Caffeine: A Comparison of Physiological Arousal Effects.* May 17, 1972. This memo attaches a report of the same name by Schori and B.W. Jones, which concludes that caffeine and nicotine, which is generally "administered by smoking," both have stimulant effects, but that the effects of caffeine are more like those of placebo than those of smoking. Pages 1, 7 of report.

Memo to T.S. Osdene from W.L. Dunn. Plans and Objectives - 1982. November 5, 1981. Memo says that Philip Morris is conducting research on the effects of nicotine on electrical activity in the brain "*on the premise that events which reinforce the smoking act are central nervous system events.*" Page 4.

BATCO documents also make clear that top company officials recognize nicotine's drug effects and recognize that the company's sales are tied to those effects. In a July 1962 meeting, Sir Charles Ellis, who served as the science advisor to the BATCO board, gave a presentation in which he affirmed the central role of nicotine in tobacco use and enthusiastically endorsed its pharmacological benefits to smokers as similar to those provided by stimulants and tranquilizers:

> *It is my conviction that nicotine is a very remarkable beneficent drug that both helps the body to resist external stress and also can as a result show a pronounced tranquilising effect. You are all aware of the very great increase in the use of artificial controls, stimulants, tranquilisers, sleeping pills, and it is a fact that under modern conditions of life people find that they cannot depend just on their subconscious reactions to meet the various environmental strains with which they are confronted: they must have drugs available which they can take when they feel the need. Nicotine is not only a very fine drug, but the techniques of administration by smoking has considerable psychological advantages and a built-in control against excessive absorption.*[190] [Emphasis added.]

Dr. Sidney J. Green, a BATCO board member as well as the firm's director of research, frequently acknowledged, in internal documents, the central role of nicotine's pharmacological effects in tobacco use. In a 1967 memo on BATCO research needs, Dr. Green pointed out that:

> *There has been significant progress in understanding why people smoke and opinion is hardening in medical circles that the pharmacological effects of nicotine play an important part and that these effects on balance may be beneficial.* [Emphasis added.][191]

In a paper on future research policy entitled "B.A.T. Group Research" (1968), Dr. Green wrote

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Dunn, WL. *Smoking as a Possible Inhibitor of Arousal.* Submitted to Philip Morris Manuscript Review Board on August 16, 1976.

[190] BATCO Research Conference. Southampton, England. Presentation by Sir Charles Ellis entitled *The Smoking and Health Problem.*1962. Pages 15-16.

[191] Green SJ. March 2, 1967, memorandum to D.S.F. Hobson entitled *Smoking and Health: Some Recent Findings.* Appendix I, page 1. In the same document at Appendix II, page 1, Dr. Green also wrote that "[t]here is now no doubt that nicotine plays a large part in the action of smoking for many smokers."

that there were four motives for smoking, at least three of which depend on the pharmacological and addictive effects of nicotine:

> *There appear to be four recognisable types of smoking behaviour:*
> *1. Habitual*
> *2. Addictive*
> *3. Enhancing desirable emotions and feelings such as enjoyment or excitement.*
> *4. Decreasing undesirable emotions and feelings such as anger, fear and shame.*[192]

In another paper a few years later, Dr. Green wrote more forcefully:

> *The tobacco smoking habit is reinforced or dependent upon the psycho-pharmacological effects mainly of nicotine.*[193]

Attorneys for some of the major U.S. tobacco manufacturers have asserted that the "benefits" of smoking include a range of significant pharmacological effects. For example, attorneys for R.J. Reynolds Tobacco Company described the following pharmacological benefits of smoking in a court filing:

> *[S]atisfaction; stress reduction; relaxation; stimulation; aided concentration; increased memory retention; alleviation of boredom and fatigue; avoidance of loss of vigilance in repetitive and sustained tasks. . .*[194]

CTR has also supported research on the psychopharmacology of nicotine and has concluded that nicotine's drug effects play an important role in why people use tobacco. CTR's annual report for 1966-67 described reports of smokers that they liked or needed to smoke

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[192] Green SJ. Lecture notes of Chelwood talk. BATCO Group Research Conference. Chelwood Vachery, England. September 4, 1968. Pages 1, 2.

[193] Green SJ. *The Association of Smoking and Disease.* July 26, 1972. Page 1.

[194] Reply to Interrogatories, *Gilboy v. American Tobacco Co. et al.,* No. 314002 (La. 19th Jud. Dist. Ct.). Attorneys for Lorillard Tobacco Company similarly characterized the pharmacological effects of smoking in a Reply to Interrogatories filed in *Covert v. Lorillard et al,* No. 88-1018-B (M.D. La):

> *Some of the benefits that are commonly reported by various smokers are. . .relaxation; relief of anxiety and stress; reduction of boredom; increased alertness; improvement in concentration. . .*

because smoking gave them a "pickup" or relaxed them.[195] The report went on to say

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[195] Report of the Scientific Director, 1966-67. Council for Tobacco Research. 1967. Page 12. CTR's annual reports disclose that the organization has funded research on nicotine's effects on the central nervous system continuously since the 1960's. *See, e.g.:*

Report of the Scientific Director, 1964-65. Council for Tobacco Research-U.S.A. Page 22:
Systematic study of the mode of action of nicotine at various synapses has been continued. Meanwhile increasing emphasis has been placed upon the psychopharmacology of nicotine . . . . Specific actions on the central nervous system have been described and the effects of these upon behavior are being sought.

Report of the Scientific Director, 1968-1969. Council for Tobacco Research-U.S.A. Page 14:
Some of the bases for human use of tobacco . . . might also be found in the realm of psycho-pharmacology, that is, in the effects of smoking and/or nicotine on the central nervous system . . . . The effects of nicotine on the brain are not always the same. Depending on the state of the nervous system and on the dosage, an "arousal" or "wake-up" effect may occur which is reflected both in brain waves and in behavior . . . . In larger doses or in a different state of the nervous system, a peculiar steady state of longer duration is produced . . . [which] has been described as a "tranquilizer effect."

Report of the Scientific Director, 1969-1970. Council for Tobacco Research-U.S.A. Page 13.
Most of the pharmacological studies currently being supported by The Council are concerned with the effects of nicotine and/or smoking on the central nervous system (the brain) with the object of learning more about why people like, want, or need to smoke.

Annual Report of The Council for Tobacco Research - U.S.A., Inc. 1971. Pages 16-17, 59 *passim.*

Report of The Council for Tobacco Research - U.S.A., Inc. 1972. Page 11.
The Council is currently supporting five studies in the field of psychopharmacology that are directed toward further elucidating the paradoxical arousal and tranquilizing effects of nicotine and its facilitation of the learning process in animals. . . . Because human smokers ordinarily receive nicotine chronically . . . a new emphasis has developed concerning habituation effects on the psychopharmacological responses to nicotine.

Report of The Council For Tobacco Research-U.S.A., Inc. 1973. Pages 13-14, 52 *passim.*

Report of the Council for Tobacco Research-U.S.A., Inc. 1974. Page 43 *passim.*

Report of the Council for Tobacco Research-U.S.A., Inc. 1975. Page 47 *passim.*

Report of the Council for Tobacco Research-U.S.A., Inc. 1977. Page 45 *passim.*

Report of the Council for Tobacco Research-U.S.A., Inc. 1978. Page 49 *passim.*

Report of the Council for Tobacco Research-U.S.A., Inc. 1979. Page 39 *passim.*

Report of the Council for Tobacco Research-U.S.A., Inc. 1981. Page 65 *passim.*

Report of the Council for Tobacco Research-U.S.A., Inc. 1982. Page 60 *passim.*

that the study of nicotine in the "new field" of psychopharmacology was providing scientific substantiation for smokers' subjective views that tobacco could both "arouse the lethargic and calm the agitated."[196]

Thus, industry documents reveal that tobacco company researchers and top officials understand and unequivocally state that nicotine is a drug and that consumers of tobacco products use them for the pharmacological effects of nicotine.

Report of the Council for Tobacco Research-U.S.A., Inc. 1983. Page 80 *passim.*

Report of the Council for Tobacco Research-U.S.A., Inc. 1984. Page 83 *passim.*

Report of the Council for Tobacco Research-U.S.A., Inc. 1985. Page 89 *passim.*

Report of the Council for Tobacco Research-U.S.A., Inc. 1986. Page 68 *passim.*

Report of the Council for Tobacco Research-U.S.A., Inc. 1987. Page 85 *passim.*

Report of the Council for Tobacco Research-U.S.A., Inc. 1988. Page 88 *passim.*

Report of the Council for Tobacco Research-U.S.A., Inc. 1990. Page 101 *passim.*

Report of the Council for Tobacco Research-U.S.A., Inc. 1991. Page 90 *passim.*

Report of the Council for Tobacco Research-U.S.A., Inc. 1992. Page 97 *passim.*

[196] *See id.*, Report of the Scientific Director, 1966-67, at p. 13.

2. Statements Recognizing That Nicotine Is Addictive

Tobacco company documents show that company researchers and executives not only have acknowledged that nicotine's pharmacological effects play a central role in consumer satisfaction with tobacco products, but have recognized nicotine's addictive properties. These documents demonstrate that tobacco companies understand that nicotine addiction is one of the major reasons that consumers use their products.

a. Tobacco Company Researchers' Views

In 1963, a report was completed for BATCO that specifically addressed the mechanism of nicotine addiction in smokers. The report, dated May 30, 1963, and titled "A Tentative Hypothesis on Nicotine Addiction,"[197] describes nicotine's effects on the brain, specifically through hypothalamo-pituitary stimulation. The report states that initially, small doses of nicotine are sufficient to trigger this mechanism, which helps people to cope with stress. However, chronic intake of nicotine, such as occurs with regular smokers, creates a situation where:

> *ever-increasing dose levels of nicotine are necessary to maintain the desired action. Unlike other dopings, such as morphine, the demand for increasing dose levels is relatively slow for nicotine.* [Emphasis added.][198]

After noting that when chronic smokers are deprived of nicotine, their endocrine system becomes unbalanced, the report states:

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[197] Haselbach C, Libert O. BATCO R&D. *A Tentative Hypothesis on Nicotine Addiction.* Southampton, England. May 30, 1963. Pages 1-3. A copy of this report was personally sent by Sir Charles Ellis of BATCO to Addison Yeaman, the General Counsel of B&W. *See* letter from Ellis to Yeaman, dated June 28, 1963.

[198] *Id.*, Haselbach et al, at p. 1.

> *A body left in this unbalanced status craves for renewed drug intake in order to restore the physiological equilibrium. This unconscious desire explains the addiction of the individual to nicotine.* [Emphasis added.][199]

The report concludes:

> *In conclusion, a tentative hypothesis for the explanation of nicotine addiction would be that of an unconscious desire to restore the normal physiological equilibrium of the corticotropin releasing system in a body in which the normal functioning of the system has been weakened by chronic intake of nicotine.* [Emphasis added.][200]

In the decades that followed this report, tobacco industry researchers repeatedly recognized nicotine's addictive properties.[201] In an article reporting on a study supported by a grant from the Tobacco Industry Research Committee (TIRC), the researcher stated that smoking is addictive:

> *Addiction to smoking is found to be consistently greater among men in military service than in civilian life, irrespective of peace or war, and greater in veterans than in nonveterans.* [Emphasis added.][202]

Similarly, a report prepared for Liggett & Myers in anticipation of the 1964 Surgeon General's Report implicitly acknowledged that nicotine dependence and withdrawal are the reasons smokers have difficulty quitting:

> *If reliance is to be placed on stopping cigarette smoking by men with warnings of high*

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[199] *Id.* at p. 2.

[200] *Id.* at p. 3.

[201] Recognition of nicotine's addictive properties apparently extended to the smokeless tobacco industry. In a Wall Street Journal article, Larry D. Story, a former U.S. Tobacco Co. (UST) chemist, was quoted as saying, "There used to be a saying at UST that 'There's a hook in every can' . . . [a]nd that hook is nicotine." Freedman AM. Juiced up: how a tobacco giant doctors snuff brands to boost their 'kick'. Wall Street Journal. October 26, 1994:A.

[202] Seltzer CC. Why people smoke. *Atlantic Monthly*. July 1962. Page 42. In a TIRC memo to the Scientific Advisory Board from R.C. Hockett, "Papers by grantees of the Tobacco Industry Research Committee," Carl Seltzer was identified as a recipient of a TIRC grant-in-aid.

> *mortality, then heavy research is badly needed . . . on means enabling such smokers to stop smoking more easily and effectively. Use of declining doses of injected nicotine or orally administered nicotine analogs during withdrawal were reported as providing some benefit . . .* [203]

In Project Wheat,[204] a study of smoking behavior conducted by BATCO, researchers concluded that consumer preferences for different cigarette types could be predicted using only two factors: 1) "Inner Need," a measure of the extent to which a smoker uses cigarettes for drug-type uses (to relieve stress, to aid concentration, as a substitute for food); and 2) concern for health. The researchers felt their conclusion to be:

> *very much in line with that made by Russell who . . . concluded that it might prove more useful to classify smokers according to their position on a single dimension of pharmacological addiction rather than in terms of their profiles on the six types of smoking.*[205]

Nicotine addiction/dependence is also acknowledged in a number of other BATCO studies and other documents.[206]

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[203] L&M Littlefield. January 17, 1963, memo from Harry B. Wissman to C.J. Kensler.

[204] *See:*
BATCO. Project Wheat - Part 1: Cluster profiles of U.K. male smokers and their general smoking habits. Southampton, England. July 10, 1975.

BATCO. Project Wheat - Part 2: U.K. male smokers: their reactions to cigarettes of different nicotine delivery as influenced by inner need. Southampton, England. January 30, 1976. (Project Wheat is described in greater detail in FINDINGS § II.C., *infra.*)

[205] *Id.*, Part 2, at p. 49.

[206] *See:*
Proceedings of the BATCO Smoking Behaviour-Marketing Conference. Session III. July 9-12, 1984. Ferris slides (BW-W2-02737-02759). One chart (BW-W2-02750), entitled *Role of Nicotine: Hypotheses*, states: "If smokers are ADDICTED to nicotine then . . . 1. The nicotine smokers get from cigarettes may be replaced by nicotine from alternative sources. 2. Cigarettes of different strengths should be smoked differently, e.g., smokers given a low/reduced delivery cigarette should smoke it more intensively (and vice versa)." [Emphasis in original.] Subsequent slides show both that nicotine replacement reduced smokers intake of cigarettes, and that cigarette consumption increased as nicotine yields decreased. Pages BW-W2-02751-02759.

In addition, a Philip Morris researcher who studied a group of smokers in a small town that had gone through a cold turkey campaign described at length the withdrawal symptoms of those who had quit smoking. Even after eight months quitters were apt to report symptoms such as feeling depressed, being restless and tense, being ill-tempered, having a loss of energy, being apt to doze off.[207] They were further troubled by constipation and weight gains which averaged about five pounds per quitter.[208] The researcher stated:

> *This is not the happy picture painted by the Cancer Society's anti-smoking commercial which shows an exuberant couple leaping in the air and kicking their heels with joy because they've kicked the habit. A more appropriate*

Armitage AK. *Appraisal of Report: "The Fate of Nicotine in the Body."* August 28, 1963. Armitage wrote:

> *The authors themselves admit (p.27) that the present results offer no conclusive evidence for any particular mechanism involved in tolerance to nicotine, nor do they indicate a lead to the phenomenon of addiction. This important problem was, I imagine, the main object of the research.*

Final Report on Project HIPPO II, note 161, *supra,* at page 4:

> *A quantitative investigation of the relations with time of nicotine - and of some possible brain mediators - on adreno-corticotrophic activity could give us the key to the explanation of both phenomena of tolerance and of addiction, in showing the symptoms of withdrawal.*

In the Minutes of the BATCO R&D Conference in Montreal (October 24, 1976), the list of "assumptions" includes the statement: "Smoking is an addictive habit attributable to nicotine." (The word "addictive" has been crossed out.) Page 2.

A report of the BATCO Group R&D Conference Part I, February 5-9, 1979, attended by Sanford and Reynolds of Brown and Williamson, under the heading "Behavioral Research," states: "With regard to dependence [the researcher] wants to study the nature and effect of dependence on smoking behavior and break smokers down into dissonant and consonant smokers." Page BW-W2-03526.

A report of the BATCO Group R&D Psychology Research (1984-86) states:

> *Activity continues in the area of researching the functional significance of smoking in everyday life, current emphasis being placed on the role of personality in relation to nicotine dependance [sic] and personal requirements of the product.* Page BW-W2-02004.

[207] Ryan FJ (Philip Morris). *Bird-1, A study of the Quit-Smoking campaign in Greenfield, Iowa, in Conjunction with Movie, Cold Turkey.* 1971. Summary, pages 30-33. *See* FINDINGS § II.C.4, *infra.*

[208] *Id.*

> *commercial would show a restless, nervous, constipated husband bickering viciously with his bitchy wife who is nagging him about his slothful behavior and growing waistline.*[209]

In his report, the Philip Morris researcher also observed that some smokers "need" tobacco, and that this need may be correlated with use of high-nicotine cigarettes.[210] In 1976, the same Philip Morris researcher elaborated on his view that smokers smoke many cigarettes to satisfy their physiological "need" for a specific level of nicotine in the blood:

> *Although nicotine intake appears a critical mainstay of tobacco consumption, not all people smoke for nicotine on all occasions . . . . All . . . cigarettes contribute to the total nicotine in the system, so that a cigarette smoked out of habit will delay the time until a cigarette is smoked out of need.*[210a]

A BATCO report, as well as a report by the American Tobacco Company, also implicitly acknowledge that nicotine produces withdrawal/physical dependence.[211]

Nicotine's capacity to produce "tolerance," often cited as a defining feature of addiction, see p. 81, is also acknowledged in several internal documents. For example, the BATCO-commissioned report "Fate of Nicotine in the Body" acknowledges that nicotine produces tolerance and/or addiction:

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[209] *Id.* at p. 33.

[210] *Id.* at p. 20.

[210a] Ryan FJ. Habit and Need Cigarettes. *In* Dunn WL. 1600/Smoker Psychology/October 1-31, 1977 [Monthly Report]. November 11, 1977. *In* 141 Cong. Rec. H7665 (daily ed. July 25, 1995).

[211] *See:*
BATCO R&D. *Relative Contributions of Nicotine and Carbon Monoxide to Human Physiological Response.* Report No. RD.839-R. November 15, 1971. Page 20:

> *All the regular smokers in this trial were required not to smoke for at least half an hour before the trials, which may have caused an additional stress factor, shown as a stimulation due to the ending of a period of forced abstinence. . .*

The American Tobacco Company, note 178, *supra,* at p. 66.

> *In addition, the alkaloid [nicotine] appears to be intimately connected with the phenomena of tobacco habituation (tolerance) and/or addiction.*

Notes from a BATCO Nicotine Conference[212] include a chart titled "Session IV -- Effects of Nicotine-interaction with the Brain (Pharmacology)." The chart includes the statement "Nicotine and smoke exposure causes adaptation of the nicotine receptor," a change that has been recognized as being associated with tolerance.

Perhaps the most telling admissions that nicotine is addictive come from marketing research studies prepared for tobacco companies. In these documents, the market researchers candidly assert nicotine's addictiveness, in a manner that appears to assume that the tobacco company recipients of the reports will not find the assertion unusual or controversial. For example, in a market research report prepared for Imperial Tobacco Ltd., on attitudes of adolescent smokers, the authors state:

> *until a certain nicotine dependence has been developed [taste] is somewhat less important than other things . . .*"[213]

Another market research firm refers to attitudes of adolescents "[o]nce addiction does take place . . ."[214] and states that "addicted they do indeed become."[215] The same firm, discussing its research on smokers' attempts to quit, reported that:

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[212] *See* Ayres note 172, *supra,* at p. BW-W2-02643.

[213] Spitzer, Mills & Bates. *The Player's Family: A Working Paper.* Report prepared for Imperial Tobacco Ltd. March 25,1977. Page 12.

[214] Kwechansky Marketing Research. *Project Plus/Minus*, in "Study Highlights." Report prepared for Imperial Tobacco Ltd. May 7, 1982.

[215] *Id.* at p. 26. This same documents notes that: "The desire to quit seems to come earlier now than before, even prior to the end of high school. In fact, it often seems to take hold as soon as the recent starter admits to himself that he is hooked on smoking. However, the desire to quit, and actually carrying it out, are two quite different things, as the would-be quitter soon learns." *Id.* in "Study Highlights."

> *Recidivism has several causes . . . . Another is the belief that after a few weeks off cigarettes, one could begin again to smoke "just a few" . . . . This "just a few" business is actually a surrender to addiction while trying to save face for an interim period, to pretend to oneself and to others that addiction is no longer present, which is nonsense.* [216]

A market research report that was widely circulated in Britain included the following editorial comment, contained in a description of smokers' views of the role played by tar and nicotine in smoking-related health problems:

> *Another idea was that nicotine and tar combined to have a harmful effect upon health (i.e., quite apart from nicotine's addictive function).*[217] [Emphasis added.]

Later in the same study, the researchers reported under the heading "Nicotine's addictive function" that:

> *Most respondents, with a bias towards men, realised that nicotine was the attribute in cigarettes causing addiction. It was also usually seen as the component providing satisfaction.*[218] [Emphasis added.]

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[216] *Id.* at p. 36-37. The same document also says, at page ii:

> *It is likely more difficult to break the ritualistic aspects of smoking than it is to overcome the physical withdrawal.*

See also an advertising strategy document prepared for Imperial Tobacco which recommends the following advertisement:

> *The chosen scene should ideally depict a pause or moment of relaxation before, during or after the activity. This moment should correspond to the physiological need for smoking.*

Publicite BCP. *Player's Filter '81 Creative Guidelines.* January 25, 1980. [Emphasis added.]

[217] *Attitudes Towards Smoking and Health.* Page 11. Transmitted by letter dated July 26, 1979, to Dr. H.E. Bentley, Imperial Tobacco Ltd., from A.H. Johnston, Market Research Manager, Carreras Rothmans Ltd.

[218] *Id.* at p. 12.

b. Tobacco Company Executives' and Senior Officials' Views

High-ranking tobacco company officials have also acknowledged that nicotine is addictive and that this is the reason why people use tobacco.[219]

For example, in the aforementioned July 1962 tobacco industry meeting, BATCO board science advisor Sir Charles Ellis stated:

Smoking is a habit of addiction.[220]

In an internal memo, the general counsel to Brown and Williamson makes the same point in clear, simple language:

Moreover, nicotine is addictive . . . . We are, then, in the business of selling nicotine, an addictive drug . . . [Emphasis added.][221]

Dr. Green, the director of research for BATCO, also repeatedly stated his view that some portion of smoking behavior was due to its addictive effects.[222] In a note to Dr. G. Hook, another scientist at BATCO, Dr. Green wrote, "If you consider Russell's study on cigarette dependence and his five types of smoking you can conceive a pattern as follows . . ." The note follows with a hand-drawn triangle symbolizing the reasons for smoking, with the three points of the triangle labeled "sensory rewards," "psychosocial rewards," and "pharmacological rewards." In the corner of the triangle near "pharmacological rewards" are

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[219] One tobacco company, which markets a cigarette brand called "Death Cigarettes," now states on the package that "cigarettes are addictive." FDA was informed on December 23, 1994, by John D. Slade, M.D., that "Death Cigarettes" stands for "Daring Enterprises Against Tobacco Hypocrisy." The company, owned by Charles and Amelie Southwood, has a post office box in Venice, CA, and an office in Marina Del Ray, CA.

[220] Ellis C. *The Smoking and Health Problem.* BATCO Research Conference. Smoking and Health-Policy on Research. Southampton, England. 1962. Page 4.

[221] Yeaman, A. Implications of Battelle Hippo I and II and the Griffith Filter. July 17, 1963. Page 4.

[222] *See* Green, note 191, *supra,* at Appendix I.

the words "addictive smoking."[223]

In a handwritten note about the likely continued success of the tobacco industry, Dr. Green wrote:

> *The main factor ensuring the continuation of the habit is the dependency induced in smokers. . . . Certainly large numbers of people will continue to smoke because they are unable to give it up. If they could they would do so. They can no longer be said to make an adult choice. And many new smokers become dependent.*[224] [Emphasis added.]

In a handwritten paper entitled "Marketing Cigarettes in the 80's," Dr. Green again stated that addiction is a major reason that people smoke. Noting various failures and constraints in the marketing of cigarettes, including a "close down in advertising" and "the U.K. tar premium,"[225] he writes:

> *Nevertheless smokers will continue - addiction . . .*
>
> *Perhaps 50-60% dissonant smokers [smokers who continue despite desire and motivation to quit] . . .*
>
> *Regard cig[arettes] as catering for addicts.*

Finally, in a paper stating that there was adequate evidence that smoking causes disease, written shortly after he retired from BATCO, Dr. Green wrote that, while it may be up to the individual, "if he is able," to decide whether to accept the "considerable risk" from smoking:

> *on behalf of those unable to make judgments such as children and addicted smokers, the social apparatus must be used to exercise value judgments on the*

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[223] Green SJ. Note to Hook G. BATCO R&D. Southampton, England. June 11, 1974. Also in the end of the triangle marked "pharmacological rewards" were "stimulation smoking" and "tranquilisation smoking."

[224] Green SJ. Transcript of handwritten note. Undated. Attached to documents, Green SJ, *Cigarette Smoking and Causality,* and Green SJ, *Smoking, Associated Diseases and Causality.*

[225] The U.K. tar premium is a tax imposed on products on the basis of tar content.

acceptability of the risks.[226] [Emphasis added.]

In 1961, Dr. Wakeham of Philip Morris noted in a presentation to the company's Research and Development Committee that "continued usage [of nicotine] develops tolerance."[227]

William Dunn, a senior scientist at Philip Morris, made numerous statements reflecting the position that nicotine has the properties of an addictive drug. In 1969, Dunn wrote a memorandum to his supervisor, entitled "Objectives and Plans - 1600," describing the research Philip Morris planned to undertake in the coming year. One of the planned research projects were designed to investigate the addictive properties of nicotine, by teaching rats:

> *to seek the inhalation of cigarette smoke . . . . ultimately through the reinforcing effect of the psychopharmacological effects of the inhaled smoke.*[227a]

As described in § I.B.3., supra, the ability of a substance to function as "positive reinforcer" in animals is one of the most significant pieces of evidence that the substance will be addictive in humans. By 1980, Dunn reported that Philip Morris researchers had successfully demonstrated that rats will self-administer nicotine,

> *making it quite clear that nicotine can function as a positive reinforcer for rats.*[227b]

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[226] Green, note 224, *supra,* at p. 92238.

[227] Wakeham, note 185, *supra.*

[227a] Dunn WL and Eichorn PA. Objectives and Plans - 1600. January 8, 1969. *In* 141 Cong. Rec. H7646 (daily ed. July 25, 1995). A second research project planned for 1969 was intended to discover "any product that can potentially replace the cigarette in need-gratification."

[227b] Memorandum to T.S. Osdene from W.L. Dunn. Plans and Objectives - 1981. November 26, 1980. *In* 141 Cong. Rec. H7682 (daily ed. July 25, 1995). Philip Morris undertook a range of animal studies on nicotine that constitute the classic methods for assessing the addictive properties of drugs, including self-administration, tolerance, and discrimination studies:

Other statements are equally revealing. A 1974 annual research report from the Behavioral Research program at Philip Morris, which was approved by Thomas Osdene (later Philip Morris' Vice President for science and technology) and distributed to the Vice President for research and development, states that people continue to smoke because the "pharmacologically active components of smoke" are "reinforcing":

> *A general premise in our model of the cigarette smoker is that the smoking habit is maintained by the reinforcing effect of the pharmacologically active components of smoke. A corollary to this premise is that the smoker will regulate his smoke intake so as to achieve his habitual quota of the pharmacological action.*[227c]

The report goes on to acknowledge that stopping smoking produces a withdrawal syndrome like that of other habit-forming drugs. Commenting on a proposed study to test the hypothesis that smoking decreases aggressivity, the researchers note that any increase in

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> *Nicotine discrimination, self-administration, and tolerance studies will enable us to examine the cueing and reinforcing properties of nicotine and nicotine analogues in rats. These are the state-of-the-art bioassays for central nervous system activity which we believe will serve as useful models of human smoking behavior.* [Emphasis added.]

Memorandum to T.S. Osdene from J.I. Seeman et al. Nicotine Program: Specific Implementation. March 31, 1978. *In* 141 Cong. Rec. H7668, *supra*. In 1980, Philip Morris decided to perform yet another study of "the rewarding properties of nicotine" using a technique developed to study the similar properties of morphine:

> *Mucha and Van der Kooy (1979) have reported that a place preference paradigm may be used to demonstrate the rewarding properties of morphine. We plan to use a similar paradigm to examine the rewarding properties of nicotine.*

Memorandum to T.S. Osdene from W.L. Dunn. Plans and Objectives-1980. January 7, 1980. *In* 141 Cong. Rec. H7671, *supra*.

[227c] Philip Morris Research Center. Behavioral Research Annual Report (Part II). *In* 141 Cong. Rec. H7660 (daily ed. July 25, 1995). Approved by T.S. Osdene and distributed to H. Wakeham et al. November 1, 1974. Philip Morris officials consistently held the view that the reinforcing properties of cigarette smoking have a pharmacological basis, as shown by a document written six years later, in which the following statement appears:

> *It is our belief that the reinforcing properties of cigarette smoking are directly relatable to the effects that smoking has on the electrical and chemical events within the central nervous system.*

Memorandum to T.S. Osdene from W.L. Dunn. Plans and Objectives-1981. November 26, 1980. *In* 141 Cong. Rec. H7681, *supra*.

aggressivity following deprivation

> *may be as readily explained as the emergence of reactions to [cigarette] deprivation, not unlike those to be observed upon withdrawal from any of a number of habituating pharmacological agents.*[227d]

A Philip Morris research report written by Dunn again acknowledged that cigarette deprivation produces a withdrawal syndrome in 1980, and stated that those smokers who suffered withdrawal in the absence of sufficient nicotine showed "nicotine dependence." The report began by stating the Philip Morris had attempted to identify

> *two smoking population subgroups, one of which has greater nicotine needs than the other. We have described these people in the past as compensators and noncompensators, and attempted to define them by their consumption changes when nicotine deliveries were moderately shifted . . . . Now we may have two extra tools to use: PM cigarettes of ultra low tar and nicotine, and salivary nicotine concentrations . . . . We therefore propose a shift study in which smokers are shifted to an ultra low brand, and the key dependent variable becomes the presence or absence of the withdrawal syndrome. Those who show evidence of nicotine dependence and those who do not can then be used to test our hypotheses on the relationship of salivary concentration to smoking behavior.*[227e] [Emphasis added.]

CTR documents also refer to the addictive properties of nicotine. In a section of its annual report for 1966-67 entitled "Nicotine and the Central Nervous System," CTR described research in which monkeys self-administered nicotine.[228]

Much more recently, tobacco companies have attempted to rely on the "common

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[227d] Behavioral Research Annual Report, Part II. Approved by T.S. Osdene. November 1, 1974. *In* 141 Cong. Rec. H7660 (daily ed. July 25, 1995).

[227e] Memorandum to T.S. Osdene from W.L. Dunn. Plans and Objectives-1980. January 7, 1980. *In* 141 Cong. Rec. H7672 (daily ed. July 25, 1995).

[228] *See* Report of the Scientific Director, 1966-67, note 195, *supra,* at pp. 12-13. As discussed earlier, it is well-established that self-administration of a substance by animals, under laboratory conditions, demonstrates that the substance is a "positive reinforcer," one of the hallmark properties of addictive drugs. *See* p. 96.

knowledge" that nicotine is addictive to defend against product liability cases brought by smokers. For example, in Rogers v. R.J. Reynolds et al., attorneys for Philip Morris, R.J. Reynolds, the American Tobacco Co., and the Liggett Group argued that the plaintiff could not claim that her deceased husband was not adequately warned that cigarettes were addictive, because their addictive properties are so well known:

> *There can be no serious suggestion that ordinary consumers do not expect to find nicotine in cigarettes, or that ordinary consumers have not long been well aware that it may be very difficult to stop smoking. [Footnote omitted.] The common knowledge of the alleged habituating or "addicting" properties of cigarettes has resulted in almost casual references to these properties in decisions from around the country throughout this century.*[229]

Finally, F. Ross Johnson, the former chief executive of RJR Nabisco, has openly acknowledged that tobacco is addictive and that its addictive properties are why people smoke. In an interview for an article in the Wall Street Journal, Mr. Johnson was asked about tobacco. He responded:

> *Of course it's addictive. That's why you smoke . . .*[230]

Accordingly, it is clear that high-ranking officials of tobacco companies have long known that nicotine is an addictive drug and, more importantly, that the market for tobacco products in large part depends on the addictive effects of nicotine.

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[229] Rogers v. R.J. Reynolds et al (Sup.Ct. Ind.)(No. 49A02-8904 CV 164)(1990), Appellees Brief in Reply to Appellants' Opposition to Petition for Transfer, at pp. 7-8.

[230] Shapiro E. Big spender finds new place to spend. *The Wall Street Journal.* October 6, 1994.

3. Statements That Tobacco Products Are Nicotine Delivery Systems

Internal and published documents also show that top-ranking tobacco industry officials intend to offer tobacco products to consumers as nicotine delivery systems. In summarizing the 1972 conference sponsored by CTR, William Dunn, Jr., of Philip Morris characterized the cigarette as a nicotine delivery system:

> *Think of the cigarette pack as a storage container for a day's supply of nicotine*
> . . . .
> *Think of the cigarette as a dispenser for a dose unit of nicotine:*
> *1) It is readily prepped for dispensing nicotine.*
> *2) Its rate of combustion meters the dispensing rate, setting an upper safe limit for a substance that can be toxic in large doses.*
> *3) Dispensing is unobtrusive to most ongoing behavior.*
>
> *Think of a puff of smoke as the vehicle of nicotine:*
> *1) A convenient 35 cc mouthful contains approximately the right amount of nicotine.*
> *2) The smoker has wide latitude in further calibration: puff volume, puff interval, depth and duration of inhalation. . . .*
> *3) Highly absorbable: 97% nicotine retention.*
> *4) Rapid transfer: nicotine delivered to blood stream in 1 to 3 minutes . . . .*
>
> *Smoke is beyond question the most optimized vehicle of nicotine and the cigarette the most optimized dispenser of smoke.*[231]

In a document entitled "RJR confidential research planning memorandum on the nature of the tobacco business and the crucial role of nicotine therein," quoted in the New York Times, RJR executive Claude Teague, Jr. wrote:

> *In a sense, the tobacco industry may be thought of as being a specialized, highly ritualized, and stylized segment of the pharmaceutical industry. Tobacco products uniquely contain and deliver nicotine, a potent drug with a*

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[231] *See* Dunn Summary, note 133, *supra*. (Indeed, when interviewed by FDA officials in May 1994, Dunn stated that he was known as "the Nicotine Kid" at Philip Morris. See handwritten notes summarizing meeting May 10, 1994, between FDA and Dr. W.L. Dunn.)

variety of physiological effects.[231a]

The memo goes on:

> *If nicotine is the sine qua non of tobacco products, and tobacco products are recognized as being attractive dosage forms of nicotine, then it is logical to design our products - and where possible our advertising - around nicotine delivery rather than around tar delivery or flavor.*[231b]

As noted above, Sir Charles Ellis, BATCO's scientific advisor, considered smoking a method of administering nicotine as early as 1962:

> *Nicotine is not only a very fine drug, but the techniques of administration by smoking has [sic] considerable psychological advantages and a built-in control against excessive absorption.*[232]

Dr. S.J. Green, BATCO board member and research director, also viewed the cigarette as a vehicle for delivering nicotine. In a document describing BATCO's research needs, he made the following statement:

> *It may be useful, therefore, to look at the tobacco industry as if for a large part its business is the administration of nicotine (in the clinical sense).*[233]

In a draft of another document entitled "A Blueprint for B.A.T. Scientific Departments," Green repeated this belief:

[231a] Hilts PJ. U.S. Convenes Grand Jury to Look at Tobacco Industry. *New York Times.* July 26, 1995.

[231b] *Id.*

[232] Ellis C. *The Smoking and Health Problem.* BATCO Research Conference. Smoking and Health-Policy on Research. Southampton, England. 1962. Page 16.

[233] Green, note 191, *supra,* at Appendix II.

See also Green, note 192, *supra,* at p. 2:

> *[w]hile other factors cannot be ignored and their influence is not completely understood, it seems a good assumption that nicotine plays a predominant role for many smokers. So that a good part of the tobacco industry is concerned with the administration of nicotine to consumers . . . . [T]hus a large part of our research problem can be identified as the improvement in quality by improving the administration of nicotine . . .*

We must assume that the main objective is the administration of nicotine . . . [234]

In a handwritten chart, attached to a paper entitled "The Association of Smoking and Disease," Green described all forms of tobacco as different methods of nicotine administration.[235]

The 1981 monograph on nicotine pharmacology and toxicology published by the British Tobacco Advisory Council expressly states that nicotine is a drug and that tobacco is simply a vehicle for its administration.[236] After setting forth the purpose of the monograph -- to help medical authorities decide whether smoking-related illness should be handled by eliminating smoking altogether, by progressively reducing smoke deliveries, or by developing a cigarette that delivers "an adequate dose of nicotine without the necessity of inhaling large doses of toxic vehicle" -- the introduction states succinctly:

> *In a nutshell our approach has been to regard nicotine as a "drug" to which man is exposed in various "vehicles" and by various routes.*[237]

A presentation at the 1984 BATCO Smoking Behaviour-Marketing Conference included the following slides:

> *Relationship Between Smoking Behaviour and Nicotine Intake*
>
> > *Is there any commonalty [sic] in the process [of smoking]:*
> > *- broad similarities in wholebody nicotine dose of nicotine across smoking groups*
> > *- strong indirect evidence of smokers smoking for nicotine*
> > *- is this cause and effect or a reflection for something else*

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[234] Undated draft of *A Blueprint for B.A.T. Scientific Departments.* Page 4.

[235] *See* Green, note 193, *supra.* Handwritten chart attached.

[236] Cohen, note 183, *supra,* at p. 1.

[237] *Id.* at p. 1. (Emphasis added.)

What is the Significance of this Observation:

> *-underlying smoking maintenance through nicotine, and as a consequence probably provides the basis of smoking satisfaction - in its simplest sense puffing behaviour is the means of providing nicotine dose in a metered fashion* [Emphasis added.][238]

Finally, in a list of expected changes in cigarettes over the next several years, a BATCO official suggested that cigarettes could become delivery systems for drugs in addition to nicotine:

> *"Increases in the use of drugs other than nicotine. Potential legalisation of the use of marijuana. Possible introduction of caffeine."* [Emphasis added.][239]

Thus, tobacco company executives have both recognized that nicotine's drug effects are central to the use of tobacco and stated their clear understanding that cigarettes are being sold to and used by smokers as nicotine delivery systems. On the basis of this evidence, these products are intended to affect the structure or function of the body.

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[238] Proceedings of the BATCO Smoking Behaviour-Marketing Conference. Session I. July 9-12, 1984. Slides.

[239] FH [Initials of BATCO employee]. BATCO R&D. *Technical and Product Developments Envisaged Over the Next Five Years.* January 22, 1974. Page 1.

B. INDUSTRY RESEARCH ON THE DRUG EFFECTS OF NICOTINE

The tobacco industry has conducted and funded extensive research to characterize nicotine's addictive potential and properties. This research includes studies on nicotine's absorption into the bodies of tobacco users, its effects on behavior, and its effects on the brain and endocrine systems.[240] Sections II.B., C., and D. detail the extensive research conducted and funded by the tobacco industry on: 1) nicotine's pharmacological effects, § II.B., infra; 2) how consumers use tobacco products to obtain an adequate dose of nicotine, § II.C., infra; and 3) how to manipulate nicotine delivery from tobacco to provide an adequate dose to consumers, § II.D., infra.[240a]

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[240] The long history of tobacco and nicotine use for pharmacological purposes is also well known to the tobacco industry. Larson PS, Silvette H. Medical uses of tobacco (past and present), (funded by a grant from the Tobacco Industry Research Committee and presented at industry-sponsored symposium). In: VonEuler, ed. *Tobacco Alkaloids and Related Compounds.* New York, NY: Pergamon Press; 1965:3-11.

See also Cohen, note 183, *supra,* at p. 1.

[240a] The extent of the industry's research on nicotine pharmacology is very likely to be even greater than that reflected in this section. According to a recent report in the New York Times, Philip Morris conducted internal research on nicotine's pharmacological effects on smokers from the late 1960's to the mid-1980's. The Times reported that Charles Wall, a Philip Morris lawyer, confirmed that company documents showed that Philip Morris carried out extensive research on nicotine over many years. Hilts PJ. "Documents Disclose Philip Morris Studied Nicotine's Effect on Body." *New York Times.* June 8, 1995. Documents later disclosed by Congress provide detailed evidence of Philip Morris' long-term research on nicotine pharmacology, including studies to isolate and characterize nicotine receptors in the central nervous system, the effects of nicotine/smoking on the electrical activity of the brain, the effects of nicotine on human and animal behavior, self-administration of nicotine by rats, nicotine discrimination in rats, nicotine tolerance, and the effects of nicotine administration on human physiologic function, including the relationship between blood nicotine levels and central nervous system activity. 141 Cong. Rec. H7470-76 (daily ed. July 24, 1995); 141 Cong. Rec. H7646-83 (daily ed. July 25, 2995). Philip Morris has not contested the authenticity of these documents. R.J. Reynolds, too, appears to have conducted extensive research on nicotine pharmacology that is not fully reflected here. In response to questions about that company's research on nicotine, a spokeswoman for R.J. Reynolds Tobacco Company stated that "[w]e've not only done research on the pharmacological effects of nicotine but we've published it in at least 250 peer-reviewed journals and symposia. We're extremely proud of the quality and number of the studies." Collins G. "Legal Attack on Tobacco Intensifies." *New York Times.* June 9, 1995.

It is important to understand why the tobacco industry has conducted this research. Tobacco industry documents show that the industry research described in the following sections was undertaken because industry officials strongly suspected, more than 30 years ago, that nicotine's pharmacological effects were vital to the successful marketing of tobacco. For example, internal BATCO documents disclose that the major BATCO-sponsored nicotine studies completed or underway in the early 1960's were undertaken "to elucidate the effects of nicotine as a beneficent alkaloid drug"[241] because of the belief of Sir Charles Ellis, the leading BATCO scientist, that "we are in a nicotine rather than a tobacco industry."[242]

Another nicotine study commissioned by BATCO in the early 1960's similarly reveals that industry research on nicotine's pharmacological effects was undertaken because of the industry's understanding that consumers use tobacco to obtain those effects:

> *There is increasing evidence that nicotine is the key factor in controlling, through the central nervous system, a number of the beneficial effects of tobacco smoke . . . . Detailed knowledge of these effects of nicotine in the body*

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[241] *See* Ellis, note 232, *supra,* at p. 16. On the same page Ellis describes upcoming research "to investigate whether cigarette smoke produces effects on the central nervous system characteristic of tranquilising or stimulating drugs and, if so, to see if such activity is due solely to nicotine."

[242] Johnson RR. *Comments on nicotine.* June 30, 1963. Pages 10-11. This document goes on to reveal that these studies on nicotine's pharmacological effects were part of a broader research initiative that was being conducted by the industry and included altering nicotine delivery:

> *The Southampton group is going to be doing a large amount of work on nicotine, and for some good reasons. To summarize:*
> *Project ARIEL [a cigarette alternative developed by BATCO] - This is dormant for the moment. The first samples tried gave a tremendous kick, even though the nicotine delivery was quite small. It would appear that the project will be reinitiated within a few months.*
> *Dr. S.R. Evelyn is presently investigating the absorption of extractable and non-extractable nicotine in the mouth . . . .*
> *Dr. J.D. Backhurst is setting up an analysis for pH of whole smoke on a puff-by-puff basis. This correlates with his previous interest in extractable nicotine.*
> *Mr. H.G. Horsewell continues to work with alkaline filter additives which selectively increase nicotine delivery.*

of a smoker is therefore of vital importance to the tobacco industry.[243]

An annual report from the Council for Tobacco Research discloses that the research it funded on nicotine's pharmacology was designed to elucidate the effects of nicotine on the smoker's central nervous system:

> *Most of the pharmacological studies currently being supported by The Council are concerned with the effects of nicotine and/or smoking on the central nervous system (the brain) with the object of learning more about why people like, want, or need to smoke.*[244]

The studies of nicotine's pharmacokinetics and pharmacodynamics described in § II.B., infra, were undertaken to assist the industry in marketing products that would satisfy tobacco users' nicotine requirements. This information relating to how nicotine acted in the body was needed by the industry for additional studies specifically designed to establish the dose of nicotine required by consumers, § II.C., infra. As noted in the report of one study whose purpose was to validate a method for assaying nicotine and a metabolite in urine:

> *It can be concluded from the comparative studies that analysis of nicotine and cotinine in urine is likely to be a good indicator of whole body nicotine dose in man. This technique has an immediate and direct relevance for . . . human behavioural studies in the assessment of an individuals' [sic] nicotine dose in response to modification in cigarette design.* [Emphasis added.][245]

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[243] Geissbuhler H, Haselbach C. *The Fate of Nicotine in the Body*. Battelle Memorial Institute. Geneva, Switzerland. May 1963. Page 1. Report prepared by Battelle for BATCO. (Hereafter cited as: BATCO. *The Fate of Nicotine in the Body*.).

[244] Report of the Scientific Director, 1969-1970. Council for Tobacco Research-U.S.A. Page 13.

[245] BATCO Group R&D Centre. *Nicotine Studies: A Second Report. Estimation of Whole Body Nicotine Dose By Urinary Nicotine and Cotinine Measurement.* Report No. RD.1792. March 31, 1981. Page 1.

Industry documents related to other basic research studies on nicotine show a similar nexus with product development. For example, the report from a 1974 Brown and Williamson study of nicotine's brain effects states that:

> *The development of new products and the modification of existing ones requires that we have some knowledge of the smoker toward whom these efforts are directed. The work described in this report is focused on the acute, or immediate physiological response of*

Thus, this research demonstrates the tobacco industry's fundamental interest in the dose of nicotine absorbed into the systemic circulation of the tobacco user (rather than simply the amount of nicotine necessary to deliver sensory effects to the mouth of the user.)

The ultimate purpose of the tobacco industry's studies on nicotine was to better understand the nicotine requirements of tobacco users and to develop products that delivered the desired pharmacological effects of nicotine. Philip Morris officials stated that the rationale for the company's extensive research program on nicotine pharmacology was that the information would

> *strengthen Philip Morris R&D capability in developing new and improved smoking products.*[245a]

Accordingly, the industry-sponsored studies described in the following sections provide further evidence that tobacco manufacturers intend to market their products to deliver the pharmacological effects of nicotine to consumers.[246]

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smokers.

Brotzge RF, Kennedy JE. Brown and Williamson. *Human Smoking Studies: Acute Effect of Cigarette Smoke on Brain Wave Alpha Rhythm - First Report.* October 31, 1974. Report No. 74-20. Page 1.

Similarly, a 1974 BATCO study on nicotine's effects on brain electrical activity was intended to "help elucidate the mode of action of nicotine during smoking" so as to better understand smoker behavior in response to nicotine. BATCO Group Research & Development. Comer AK, Thornton RE. *Interaction of Smoke and the Smoker Part 3: The Effect of Cigarette Smoking on the Contingent Negative Variation.* Report No. RD.1164-R. December 12, 1974. Page 2.

[245a] Memorandum from W.L. Dunn to T.S. Osdene-Plans and Objectives-1979. December 6, 1978. *In* 141 Cong. Rec. H7669 (daily ed. July 25, 1995).

[246] The full citations for the references in notes 247 through 279 can be found in Appendix 4. Entries under the heading "OTHER" include studies sponsored by the Smokeless Tobacco Research Council (whose members include U.S. tobacco companies), Swedish Tobacco Co. (which has corporate relationships with both Pinkerton and U.S. Tobacco Co.), Svenska Tobaks (a subsidiary of Swedish Tobacco Co.), the Tobacco Advisory Council and the Tobacco Research Council of the U.K. (whose members included British-American Tobacco Co.), Imperial Tobacco Co. (which has corporate relationships with British-American Tobacco Co., and manufactures cigarettes that are marketed in the U.S.), Carreras Rothmans Ltd. (whose affiliated companies manufacture cigarettes that are marketed in the U.S.), Swiss Association of Cigarette Manufacturers (whose members include affiliates of U.S. tobacco companies, and the Canadian Tobacco Manufacturers Council (whose members include affiliates of U.S. tobacco companies).

1. Industry Research on Nicotine's Effects on the Brain

The tobacco industry has extensively studied, in its own laboratories and through grants or contracts to other laboratories, the effects of nicotine on the brain and other parts of the central nervous system, including the sites in the brain on which nicotine acts.[247]

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[247] COUNCIL FOR TOBACCO RESEARCH-USA

Abood. Comparison of the binding of optically pure (-)- and (+)-[3H]nicotine to rat brain membranes

Abood. Electrophysiological, behavioral, and chemical evidence for a noncholinergic, stereospecific site for nicotine in rat brain

Abood. Receptor binding characteristics of a 3H-labeled azetidine analogue of nicotine

Abood. Tritiated methylcarbamylcholine a new radioligand for studying brain nicotinic receptors

Abood. Evidence for a noncholinergic site for nicotine's action in brain: Psychopharmacological, electrophysiological and receptor binding studies

Abood. Acute and chronic effects of nicotine in rats and evidence for a non-cholinergic site of action

Andersson. Involvement of D1 dopamine receptors in the nicotine-induced neuro- endocrine effects and depletion of diencephalic catecholamine stores in the male rat

Andersson. Effects of acute central and peripheral administration of nicotine on hypothalamic catecholamine nerve terminal systems and on the secretion of adenohypophyseal hormones in the male rat

Andersson. Interactions of nicotine and pentobarbitone in the regulation of telencephalic and hypothalamic catecholamine levels and turnover and of adenohypophyseal hormone secretion in the normal male rat

Andersson. Effects of single injections of nicotine on the ascending dopamine pathways in the rat

Andersson. Mecamylamine induced blockade of nicotine induced inhibition of gonadotrophin and TSH secretion and of nicotine induced increases of catecholamine turnover in the rat hypothalamus

Andersson. Nicotine-induced increases of noradrenaline turnover in discrete noradrenaline nerve terminal systems of the hypothalamus and the median eminence of the rat and their relationship to changes in the secretion of adenohypophyseal hormones

Andersson. Involvement of cholinergic nicotine-like receptors as modulators of amine turnover in various types of hypothalamic dopamine and noradrenaline nerve terminal systems and of prolactin, LH, FSH and TSH secretion in the castrated male rat

Andersson. Effects of acute intermittent exposure to cigarette smoke on catecholamine levels and turnover in various types of hypothalamic DA and NA nerve terminal systems as well as on the secretion of adenohypophyseal hormones and corticosterone

Andersson. Effects of chronic exposure to cigarette smoke on amine levels and turnover in various hypothalamic catecholamine nerve terminal systems and on the secretion of pituitary hormones in the male rat

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Davies. Evidence for a noncholinergic nicotine receptor on human phagocytic leukocytes

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Erwin. Nicotine alters catecholamines and electrocortical activity in perfused mouse brain

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Grenhoff. Selective stimulation of limbic dopamine activity by nicotine

Grenhoff. Chronic continuous nicotine treatment causes decreased burst firing of nigral dopamine neurons in rats partially hemitransected at the meso-diencephalic junction

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Harsing. Dopamine efflux from striatum after chronic nicotine: evidence for autoreceptor desensitization

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Marks. Characterization of nicotine binding in mouse brain and comparison with the binding of alpha-bungarotoxin and quinuclidinyl benzilate

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Marty. Effects of nicotine on beta-endorphin, alpha MSH, and ACTH secretion by isolated perfused mouse brains and pituitary glands, in vitro

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Toth. Effect of nicotine on extracellular levels of neurotransmitters assessed by microdialysis in various brain regions: role of glutamic acid

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Copeland. A comparison of the binding of nicotine and nornicotine stereoisomers to nicotinic binding sites in rat brain cortex

Mechanisms of action: receptors, neurotransmitters, and hormones. The tobacco industry has supported sophisticated studies to identify the sites and mechanisms of nicotine's actions, as well as how the structure of the brain itself is altered by nicotine's effects on nicotinic receptors. These studies have identified the receptors in the central nervous system on which nicotine acts; shown that nicotinic receptors present in the brain of both animals and man mediate the behavioral effects of nicotine; and sought to define the location and functional properties of these nicotinic receptors in the central nervous system.[248]

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Slotkin. Effects of prenatal nicotine exposure on neuronal development: selective actions on central and peripheral catecholaminergic pathways

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Andersson. Effects of acute central and peripheral administration of nicotine on ascending dopamine pathways in the male rat brain Evidence for nicotine induced increases of dopamine turnover in various telencephalic dopamine nerve terminal systems

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Wesnes. The separate and combined effects of scopolamine and nicotine on human information processing

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Adem. Quantitative autoradiography of nicotinic receptors in large cryosections of human brain hemispheres

Adem. Distribution of nicotinic receptors in human thalamus as visualized by 3H-nicotine and 3H-acetylcholine receptor autoradiography

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Neurotransmitters. Tobacco industry studies have shown that nicotine and its metabolites produce neurochemical and metabolic effects in the brain.[249]

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Andersson. Mecamylamine pretreatment counteracts cigarette smoke induced changes in hypothalamic catecholamine neuron systems and in anterior pituitary function

Andersson. Intravenous injections of nicotine induce very rapid and discrete reductions of hypothalamic catecholamine levels associated with increases of ACTH, vasopressin and prolactin secretion

Andersson. Involvement of cholinergic nicotine-like receptors as modulators of amine turnover in various types of hypothalamic dopamine and noradrenaline nerve terminal systems and of prolactin, LH, FSH and TSH secretion in the castrated male rat

Andersson. Interactions of nicotine and pentobarbitone in the regulation of telencephalic and hypothalamic catecholamine levels and turnover and of adenohypophyseal hormone secretion in the normal male rat

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Harsing. Dopamine efflux from striatum after chronic nicotine: evidence for autoreceptor desensitization

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These studies show that nicotine exerts its behavior modifying effects, in part, through the cascade of effects that are produced through nicotine's actions on existing brain chemicals. Industry-supported studies show that nicotine, like other addictive drugs, acts on dopaminergic receptors[250] in the mesolimbic system to release

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Mitchell. Role of the locus coeruleus in the noradrenergic response to a systemic administration of nicotine

Naftchi. Acute reduction of brain substance P induced by nicotine

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Toth. Effect of nicotine on extracellular levels of neurotransmitters assessed by microdialysis in various brain regions: role of glutamic acid

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Joseph. Possible mechanisms underlying beneficial effects of nicotine in cognitive function

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Rosecrans. Effects of nicotine on behavioral arousal and brain 5-hydroxytryptamine function in female rats selected for differences in activity

Schechter. Nicotine as a discriminative stimulus in rats depleted of norepinephrine or 5-hydroxytryptamine

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Armitage. Effects of nicotine on electrocortical activity and acetylcholine release from the cat cerebral cortex

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Slotkin. Effects of prenatal nicotine exposure on neuronal development: selective actions on central and peripheral catecholaminergic pathways

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Andersson. Effects of single injections of nicotine on the ascending dopamine pathways in the rat. Evidence for increases of dopamine turnover in the mesostriatal and mesolimbic dopamine neurons

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Erwin. Nicotine alters catecholamines and electrocortical activity in perfused mouse brain

dopamine, a chemical in the brain associated with pleasurable feelings.

Mood modification and EEG effects. In tobacco industry-sponsored trials, nicotine has been shown to induce both behavioral arousal and calming effects.[251] These effects have been correlated with

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Fuxe. Increases in dopamine utilization in certain limbic dopamine terminal populations after a short period of intermittent exposure of male rats to cigarette smoke

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Harsing. N-type calcium channels are involved in the dopamine releasing effect of nicotine

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Joseph. Possible mechanisms underlying beneficial effects of nicotine in cognitive function

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Adem. Quantitative autoradiography of nicotinic receptors in large cryosections of human brain hemispheres

Andersson. Effects of acute central and peripheral administration of nicotine on ascending dopamine pathways in the male rat brain. Evidence for nicotine-induced increases of dopamine turnover in various telencephalic dopamine nerve terminal systems

Fuxe. Regulation of endocrine function by the nicotinic cholinergic receptor

Grenhoff. Nicotinic effects on the firing pattern of midbrain dopamine neurons

Nisell. Systemic nicotine-induced dopamine release in the rat nucleus accumbens is regulated by nicotinic receptors in the ventral tegmental area

[251] **COUNCIL FOR TOBACCO RESEARCH-USA**
Domino. Electroencephalographic and behavioral arousal effects of small doses of nicotine: A neuropsychopharmacological study

Heimstra. The effects of deprivation of cigarette smoking on psychomotor performance

Marks. Genetics of nicotine response in four inbred strains of mice

Nelsen. Improvement of performance on an attention task with chronic nicotine treatment in rats

Pradhan. Effects of nicotine on several schedules of behavior in rats

Schaeppi. Nicotine treatment of selected areas of the cat brain: effects upon EEG and autonomic system

Stadnicki. Nicotine infusion into the fourth ventricle of unrestrained cats: changes in EEG and behavior

Stadnicki. Nicotinic changes in EEG and behavior after intravenous infusion in awake unrestrained cats

Yamamoto. Nicotine-induced EEG and behavioral arousal

COUNCIL FOR TOBACCO RESEARCH-USA, Literature Review
Silvette. The actions of nicotine on central nervous system functions

R. J. REYNOLDS COMPANY
Lippiello. Properties of putative nicotine receptors identified on cultured cortical neurons

Pritchard. Electroencephalographic effects of cigarette smoking

Robinson. The role of nicotine in tobacco use

BRITISH-AMERICAN TOBACCO COMPANY, LTD.
Golding. Arousing and de-arousing effects of cigarette smoking under conditions of stress and mild sensory isolation

Mangan. The effects of cigarette smoking on vigilance performance

BRITISH-AMERICAN TOBACCO COMPANY, LTD. Unpublished
Corner. Interaction of Smoke and the Smoker Part 3: The Effect of Cigarette Smoking on the Contingent Negative Variation

Thornton. Some "Benefits" of Smoking

INDUSTRY SUPPORTED SYMPOSIA
Joseph. Possible mechanisms underlying beneficial effects of nicotine in cognitive function

Wesnes. The effects of cigarette smoking and nicotine tablets upon human attention

INDUSTRY SUPPORTED AMA/ERF STUDIES
Rosecrans. Effects of nicotine on behavioral arousal and brain 5-hydroxytryptamine function in female rats selected for differences in activity

TOBACCO RESEARCH COUNCIL LABS., U.K.
Armitage. Effects of nicotine on electrocortical activity and acetylcholine release from the cat cerebral cortex

Armitage. Nicotine, smoking and cortical activation

Hall. Effects of nicotine and tobacco smoke on the electrical activity of the cerebral cortex and olfactory bulb

Morrison. Antagonism by antimuscarinic and ganglion-blocking drugs of some of the behavioural effects of nicotine

Morrison. The occurrence of tolerance to a central depressant effect of nicotine

Warwick. Experimental studies of the behavioural effects of nicotine

OTHER

electroencephalogram/electrocorticogram changes in electrical activity in the brain.[252] Whether nicotine provides a stimulating or calming effect depends on the dose of nicotine taken, the time elapsed since the last dose, and other factors.[253]

Cohen. Monograph on the "Pharmacology and Toxicology of Nicotine and its Role in Tobacco Smoking Draft

Edwards. Evidence of more rapid stimulus evaluation following cigarette smoking

Golding. Effects of cigarette smoking on measures of arousal, response suppression, and excitation/inhibition balance

Nordberg. Effect of nicotine on passive avoidance behaviour and motoric activity in mice

[252] **COUNCIL FOR TOBACCO RESEARCH-USA**
Domino. Electroencephalographic and behavioral arousal effects of small doses of nicotine: A neuropsychopharmacological study

Erwin. Nicotine alters catecholamines and electrocortical activity in perfused mouse brain

Kawamura. Differential actions of m and n cholinergic agonists on the brainstem activating system

Marty. Effects of nicotine on beta-endorphin, alpha MSH, and ACTH secretion by isolated perfused mouse brains and pituitary glands, in vitro

Nelsen. Chronic nicotine treatment in rats 2 Electroencephalographic amplitude and variability changes occurring within and between structures

Schaeppi. Nicotine treatment of selected areas of the cat brain: effects upon EEG and autonomic system

Stadnicki. Nicotine infusion into the fourth ventricle of unrestrained cats: changes in EEG and behavior

Stadnicki. Nicotinic changes in EEG and behavior after intravenous infusion in awake unrestrained cats

Yamamoto. Nicotine-induced EEG and behavioral arousal

COUNCIL FOR TOBACCO RESEARCH-USA, Literature Review
Silvette. The actions of nicotine on central nervous system functions

PHILIP MORRIS TOBACCO COMPANY
Mangan. Relationships between photic driving, nicotine and memory

(One Philip Morris document explains why the company decided to conduct nicotine-related EEG research: "We are establishing an EEG laboratory in search of the reinforcing event. Brain waves are neuro-physiological phenomena, but they are legitimate subject matter for us in that brain events underlie behavioral events. Smoke-related changes in brain waves can give us clues as to smoke-related psychological changes." Philip Morris employee (almost certainly W.L. Dunn). *Smoker Psychology Program Review*. October 19, 1977. Page 9.)

R. J. REYNOLDS COMPANY
Gilbert. Effects of smoking/nicotine on anxiety, heart rate, and lateralization of EEG during a stressful movie

Pritchard. Flexible effects of quantified cigarette-smoke delivery on EEG dimensional complexity

Pritchard. Electroencephalographic effects of cigarette smoking

Robinson. Psychopharmacological effects of smoking a cigarette with typical "tar" and carbon monoxide yields but minimal nicotine

BROWN AND WILLIAMSON TOBACCO CORPORATION, Unpublished
Brotzge. Human smoking studies: acute effect of cigarette smoke on brain wave alpha rhythm-first report

BRITISH-AMERICAN TOBACCO COMPANY, LTD.
Golding. Effects of cigarette smoking on resting EEG, visual evoked potentials and photic driving

Golding. Arousing and de-arousing effects of cigarette smoking under conditions of stress and mild sensory isolation

Golding. Effects of cigarette smoking on measures of arousal, response suppression, and excitation/inhibition balance

BRITISH-AMERICAN TOBACCO COMPANY, LTD, Unpublished
Comer. Interaction of smoke and the smoker. Part 3: The effect of cigarette smoking on the contingent negative variation

Willey. Effects of nicotine on the central nervous system

INDUSTRY SUPPORTED AMA/ERF STUDIES
Murphree. Elecroencephalographic changes in man following smoking

TOBACCO RESEARCH COUNCIL LABS., U.K.
Armitage. Effects of nicotine on electrocortical activity and acetylcholine release from the cat cerebral cortex

Armitage. The effects of nicotine on the electrocorticogram and spontaneous release of acetylcholine from the cerebral cortex of the cat

Armitage. Pharmacological basis for the tobacco smoking habit

Ashton. The use of event-related slow potentials of the brain as a means to analyse the effects of cigarette smoking and nicotine in humans

Hall. Effects of nicotine and tobacco smoke on the electrical activity of the cerebral cortex and olfactory bulb

OTHER
Edwards. Smoking, nicotine and electrocortical activity

Knott. Effects of cigarette smoking on subjective and brain evoked responses to electrical pain stimulation

Knott. Reaction time, noise distraction and autonomic responsivity in smokers and non-smokers

[253] **INDUSTRY SUPPORTED AMA/ERF STUDIES**
Rosecrans. Effects of nicotine on behavioral arousal and brain 5-hydroxytryptamine function in female rats selected for differences in activity

R. J. REYNOLDS COMPANY
Robinson. Psychopharmacological effects of smoking a cigarette with typical "tar" and carbon monoxide yields but minimal nicotine

BRITISH-AMERICAN TOBACCO COMPANY, LTD.
Mangan. The effects of cigarette smoking on vigilence performance

Effects on performance and behavior. Industry-funded scientists have conducted research to characterize nicotine's effects on behavioral performance and cognitive function.[254]

COUNCIL FOR TOBACCO RESEARCH-USA
Domino. Electroencephalographic and behavioral arousal effects of small doses of nicotine: A neuropsychopharmacological study

Marks. Genetics of nicotine response in four inbred strains of mice

Pradhan. Effects of nicotine on several schedules of behavior in rats

Yamamoto. Nicotine-induced EEG and behavioral arousal

TOBACCO RESEARCH COUNCIL LABS, U.K.
Warwick. Experimental studies of the behavioral effects of nicotine

[254] **COUNCIL FOR TOBACCO RESEARCH-USA**
Bhagat. Effect of nicotine on the swimming endurance of rats

Heimstra. The effects of deprivation of cigarette smoking on psychomotor performance

Levin. Memory enhancing effects of nicotine

Marks. Genetics of nicotine response in four inbred strains of mice

Nelsen. Chronic nicotine treatment in rats

Nelsen. Protection by nicotine from behavioral disruption caused by reticular formation stimulation in the rat

Nelsen. Improvement of performance on an attention task with chronic nicotine treatment in rats

COUNCIL FOR TOBACCO RESEARCH-USA, Literature Reviews
Essman. Drug effects and learning and memory processes

Silvette. The actions of nicotine on central nervous system functions

PHILIP MORRIS TOBACCO COMPANY
Colrain. Effects of post-learning smoking on memory consolidation.

DeNoble. Behavioral effects of intraventricularly administered (-)-nicotine on fixed ratio schedules of food presentation in rats

Mangan. Relationships between photic driving, nicotine and memory

Woodson. Effects of nicotine on the visual evoked response

R. J. REYNOLDS COMPANY
Pritchard. Enhancement of continuous performance task reaction time by smoking in non-deprived smokers

Pritchard. Electroencephalographic effects of cigarette smoking

BRITISH-AMERICAN TOBACCO COMPANY, LTD.
Mangan. The effects of cigarette smoking on vigilance performance

Mangan. The effects of smoking on memory consolidation

INDUSTRY SUPPORTED AMA/ERF STUDIES
Schechter. C.N.S. effect of nicotine as the discriminative stimulus for the rat in a T-maze

TOBACCO RESEARCH COUNCIL LABS., U.K.
Armitage. Pharmacological basis for the tobacco smoking habit

Balfour. A possible role for the pituitary-adrenal system in the effects of nicotine on avoidance behaviour

Morrison. Effects of nicotine on motor co-ordination and spontaneous activity in mice

Morrison. The effects of nicotine on punished behaviour

Warwick. Experimental studies of the behavioral effects of nicotine

Wesnes. Effects of nicotine on stimulus sensitivity and response bias in a visual vigilance task

Wesnes. The separate and combined effects of scopolamine and nicotine on human information processing

Wesnes. Effects of scopolamine and nicotine on human rapid information processing performance

Wesnes. Effects of smoking on rapid information processing performance

TOBACCO RESEARCH COUNCIL, UK, Literature Reviews
Hall. New evidence for a relationship between tobacco smoking, nicotine dependence, and stress

Wesnes. Smoking, nicotine and human performance

OTHER
Andersson. Effects of cigarette smoking on incidental memory

Battig. The effect of pre- and post-trial application of nicotine on the 12 problems of the Hebb-Williams-test in the rat

Driscoll. Effects of nicotine on the shuttlebox behavior of trained guinea pigs

Hasenfratz. Action profiles of smoking and caffeine: Stoop effect, EEG, and peripheral physiology

Hasenfratz. Can smoking increase attention in rapid information processing during noise?

Knott. Reaction time, noise distraction and autonomic responsivity in smokers and non-smokers

Knott. Noise and task induced distraction effects on information processing: Sex differences in smokers and non-smokers

Nordberg. Effect of nicotine on passive avoidance behaviour and motoric activity in mice

Roth. Smoking deprivation in "early" and "late" smokers and memory functions

Neuroendocrine effects. Tobacco industry-supported studies have demonstrated that nicotine affects hormone secretion and several endocrine functions involved in modulation of mood and behavior. These studies showed that nicotine stimulates the secretion of corticosteroids and catecholamines and decreases the secretion of thyroid stimulating hormone, leutinizing hormone, and prolactin.[255]

2. Industry Research on Nicotine Delivery to the Blood and Brain

The tobacco industry has studied the bioavailability of nicotine in tobacco products and how nicotine is distributed throughout the body, after absorption into the bloodstream. This has led to the industry's development of sophisticated techniques for determining, quantitatively and qualitatively, the presence of nicotine and its metabolites in body fluids.[256]

Wesnes. The effects of cigarettes of varying yield on rapid information processing

[255] COUNCIL FOR TOBACCO RESEARCH-USA
Andersson. Involvement of D1 dopamine receptors in the nicotine-induced neuro-endocrine effects and depletion of diencephalic catecholamine stores in the male rat

Andersson. Effects of withdrawal from chronic exposure to cigarette smoke on hypothalamic and preoptic catecholamine nerve terminal systems and on the secretion of pituitary hormones in the male rat

Andersson. Nicotine-induced increases of noradrenaline turnover in discrete noradrenaline nerve terminal systems of the hypothalamus and the median eminence of the rat and their relationship to changes in the secretion of adenohypophyseal hormones

Andersson. Mecamylamine induced blockade of nicotine induced inhibition of gonadotrophin and TSH secretion and of nicotine induced increases of catecholamine turnover in the rat hypothalamus

Andersson. Effects of acute intermittent exposure to cigarette smoke on catecholamine levels and turnover in various types of hypothalamic DA and NA nerve terminal systems as well as on the secretion of adenohypophyseal hormones and corticosterone

Andersson. Involvement of cholinergic nicotine-like receptors as modulators of amine turnover in various types of hypothalamic dopamine and noradrenaline nerve terminal systems and of prolactin, LH, FSH and TSH secretion in the castrated male rat

Andersson. Effects of acute central and peripheral administration of nicotine on hypothalamic catecholamine nerve terminal systems and on the secretion of adenohypophyseal hormones in the male rat

Fuxe. Neuroendocrine actions of nicotine and of exposure to cigarette smoke: medical implications

Fuxe. Neurochemical mechanisms underlying the neuroendocrine actions of nicotine: focus on the plasticity of central cholinergic nicotinic receptors

Fuxe. Effects of Nicotine and exposure to cigarette smoke on discrete dopamine and noradrenaline nerve terminal systems of the telencephalon and diencephalon of the rat: Relationship to reward mechanisms and neuroendocrine functions and distribution of nicotinic binding sites in brain

Marty. Effects of nicotine on beta-endorphin, alpha MSH, and ACTH secretion by isolated perfused mouse brains and pituitary glands, in vitro
Rubin.
Nicotine-induced stimulation of steroidogenesis in adrenocortical cells of the cat

Siegel. Rapid and discrete changes in hypothalamic catecholamine nerve terminal systems induced by audiogenic stress, and their modulation by nicotine-relatinship to neuroendocrine function

Westfall. Effect of 4.4'-biphenylenebis-[(2-oxoethylene)-bis-(2,2'-diethoxyethyl)] dimethylammonium dibromide (DMAE) on accumulation and nicotine-induced release of norepinephrine in the heart

Westfall. Specificity of blockade of the nicotine-induced release of 3H-norepinephrine from adrenergic neurons of the guinea-pig heart by various pharmacological agents

R. J. REYNOLDS COMPANY
Mitchell. Regionally specific effects of acute and chronic nicotine on rates of catecholamine and 5-hydroxytryptamine synthesis in rat brain

TOBACCO RESEARCH COUNCIL LABS., U.K.
Balfour. A possible role for the pituitary-adrenal system in the effects of nicotine on avoidance behaviour

OTHER
Fuxe. Regulation of endocrine function by the nicotinic cholinergic receptor

[256] AMERICAN TOBACCO COMPANY
Castro. Nicotine antibodies: comparison of ligand specificities of antibodies produced against two nicotine conjugates

COUNCIL FOR TOBACCO RESEARCH-USA
Castro. Nicotine enzyme immunoassay

Castro. Radioimmunoassays of drugs of abuse in humans: a review

Haines. Radioimmunoassay of plasma nicotine in habituated and naive smokers

McNiven. Determination of nicotine in smokers' urine by gas chromatography

Monji. Plasma nicotine pharmacokinetics in dogs after intravenous administration: determination by radioimmunassay

R. J. REYNOLDS COMPANY
Caldwell. Characterization of the glucuronide conjugate of cotinine: a previously unidentified major metabolite of nicotine in smokers' urine

Nicotine pharmacokinetics. Numerous publications document the tobacco industry's involvement in investigating all aspects of the pharmacokinetics of nicotine. (Pharmacokinetics is the study of the absorption, distribution, metabolism, and elimination of drugs in the body.) Areas that the industry has researched include:

- general pharmacokinetics of nicotine (absorption, distribution, metabolism, elimination);[257]

Davis. The determination of nicotine and cotinine in plasma

Kyerematen. Radiometric high performance liquid chromatographic assay for nicotine and twelve of its metabolites

Kyerematen. Pharmacokinetics of nicotine and 12 metabolites in the rat

Langone. Idiotype-anti-idiotype hapten immunoassays: assay for cotinine

McManus. A new quantitative thermospray LC-MS method for nicotine and its metabolites in biological fluids

BRITISH-AMERICAN TOBACCO COMPANY, Unpublished
Backhurst. Further work on extractable nicotine

Isaac. The absorption and effects of nicotine from inhaled tobacco smoke

Read. Method for nicotine and cotinine in blood and urine

Read. Nicotine studies: A second report. Estimation of whose body nicotine dose by urinary nicotine and contine measurement

BRITISH-AMERICAN TOBACCO COMPANY, LTD. Funded -- Battelle Unpublished Studies
Geissbuhler. The fate of nicotine in the body

Haselbach. A tentative hypothesis on nicotine addiction

TOBACCO RESEARCH COUNCIL LABS., U.K.
Armitage. The transfer of endogenous and exogenous radioisotopically labelled nicotine to mainstream cigarette smoke and its absorption into the blood of anaesthetized cats

Beckett. Analysis of nicotine-1-N-oxide in urine, in the presence of nicotine and cotinine, and its application to the study of in vivo nicotine metabolism in man

OTHER
Biber. Determination of nicotine and cotinine in human serum and urine: an interlaboratory study

Isaac. Cigarette smoking and plasma levels of nicotine

Schievelbein. Nicotine Workshop

Schmiterlow. Distribution of Nicotine in the Central Nervous System

Schmiterlow. Tissue distribution of C14-nicotine and Related Compounds

Szuts. Long-term fate of [14C]nicotine in the mouse: retention in the bronchi, melanin-containing tissues and urinary bladder wall

[257] **COUNCIL FOR TOBACCO RESEARCH-USA**
Becker. Studies on nicotine absorption during pregnancy

Haines. Radioimmunoassay of plasma nicotine in habituated and naive smokers

Hibberd. Enzymology of the metabolic pathway from nicotine to cotinine, in vitro

Kershbaum. Cigarette, cigar, and pipe smoking. Some differences in biochemical effects

Monji. Plasma nicotine pharmacokinetics in dogs after intravenous administration: determination by radioimmunoassay

Rama. Distribution and Retention of nicotine and its major metabolite cotinine in the rat as a function of time

COUNCIL FOR TOBACCO RESEARCH-USA, Literature Reviews
Larson. Tobacco -- Experimental and Clinical Studies

Larson. Tobacco -- Experimental and Clinical Studies -- A Comprehensive Account of the World Literature -- Supplement I

Larson. Tobacco -- Experimental and Clinical Studies -- A Comprehensive Account of the World Literature -- Supplement II

Larson. Tobacco -- Experimental and Clinical Studies -- A Comprehensive Account of the World Literature --Supplement III

AMERICAN TOBACCO COMPANY
Haag. Studies on the fate of nicotine in the body I: The effect of pH on the urinary excretion of nicotine by tobacco smokers

Larson. Studies on the fate of nicotine in the body VI: Observations on the relative rate of elimination of nicotine by the dog, cat, rabbit and mouse

Larson. Studies on the fate of nicotine in the body II: On the fate of nicotine in the dog

Larson. Studies on the fate of nicotine in the body IV: Observations on the chemical structure of an end product of nicotine metabolism

McKennis. N-methylation of nicotine and cotinine in vivo

Owen. Studies on the fate of nicotine in the animal body. VIII: Observations on the number and chemical nature of nicotine metabolites in the dog and cat

Weatherby. Rate of elimination of nicotine by the rabbit

R. J. REYNOLDS COMPANY
Caldwell. Characterization of the glucuronide conjugate of cotinine: a previously unidentified major metabolite of nicotine in smokers' urine

Caldwell. Intragastric nitrosation of nicotine is not a significant contributor to nitrosamine exposure

deBethizy. Chemical and biological studies of a cigarette that heats rather than burns tobacco

deBethizy. Absorption of nicotine from a cigarette that does not burn tobacco

- factors affecting the absorption of nicotine into the bloodstream, including route of administration;[258]
- distribution of nicotine to the brain;[259] and

Hammond. Metabolism of nicotine by rat liver cytochromes P-450: Assessment utilizing monoclonal antibodies to nicotine and cotinine

Kyeremateu. Pharmacokinetics of nicotine and 12 metabolites in the rat

Kyeremateu. Disposition of nicotine and eight metabolites in smokers and nonsmokers: Identification in Smokers of two metabolites that are longer lived than cotinine

BROWN AND WILLIAMSON TOBACCO CORPORATION, Unpublished
Brotzge. Human smoking studies: acute effect of cigarette smoke on brain wave alpha rhythm - first report

BRITISH-AMERICAN TOBACCO COMPANY, LTD., Funded - - Unpublished Battelle Studies
Geissbuhler. The fate of nicotine in the body

TOBACCO RESEARCH COUNCIL LABS., U.K.
Armitage. Absorption and metabolism of nicotine from cigarettes

Armitage. Absorption of nicotine in cigarette and cigar smoke through the oral mucosa

Armitage. The transfer of endogenous and exogenous radioisotopically labelled nicotine to mainstream cigarette smoke and its absorption into the blood of anaesthetized cats

Beckett. Effect of smoking on nicotine metabolism in vivo in man

Beckett, Analysis of nicotine-1-N-oxide in urine, in the presence of nicotine and cotinine, and its application to the study of in vivo nicotine metabolism in man

Beckett. Buccal absorption of basic drugs and its application as an in vivo model of passive drug transfer through lipid membranes

Jenner. Species variation in the metabolism of R-(+)- and S-(-)-nicotine by alpha-C- and N-oxidation in vitro

Jenner. Factors affecting the in vitro metabolism of R-(+)- and S-(-)-nicotine by guinea-pig liver preparations

OTHER
Cholerton. Sources of inter-individual variability in nicotine pharmacokinetics

Cohen. Monograph on the Pharmacology and Toxicology of Nicotine and its Role in Tobacco Smoking

Hasenfratz. Development of central and peripheral smoking effects over time

Pilotti. Studies on the identification of tobacco alkaloids, their mammalian metabolites and related compounds by gas chromatography- -mass spectrometry

Schievelbein. Nicotine Workshop

Schmiterlow. Tissue distribution of C14-nicotine

Schmiterlow. Distribution of nicotine in the central nervous system

Szuts. Long-term fate of [14C]nicotine in the mouse: retention in the bronchi, melanin-containing tissues and urinary bladder wall

[258] **COUNCIL FOR TOBACCO RESEARCH-USA**
Haines. Radioimmunoassay of plasma nicotine in habituated and naive smokers

Kershbaum. Cigarette, cigar, and pipe smoking. Some differences in biochemical effects

R. J. REYNOLDS COMPANY
deBethizy. Chemical and biological studies of a cigarette that heats rather than burns tobacco

deBethizy. Absorption of nicotine from a cigarette that does not burn tobacco

BRITISH-AMERICAN TOBACCO COMPANY, LTD. Unpublished
Backhurst. Further Work on Extractable Nicotine

Evelyn. Retention of nicotine and phenols in the human mouth

Evelyn. Transfer of nicotine from smoke into blood using a perfused canine lung

Evelyn. Absorption of nicotine via the mouth: studies using animal models

Isaac. The absorption and effects of nicotine from inhaled tobacco smoke

TOBACCO RESEARCH COUNCIL LABS., U.K.
Armitage. Absorption of nicotine by man during cigar smoking [proceedings]

Armitage. Absorption of nicotine from small cigars

Armitage. The transfer of endogenous and exogenous radioisotopically labelled nicotine to mainstream cigarette smoke and its absorption into the blood of anaesthetized cats

Armitage. Absorption of nicotine in cigarette and cigar smoke through the oral mucosa

OTHER
Hasenfratz. Development of central and peripheral smoking effects over time

Schievelbein. Nicotine workshop: Absorption of nicotine under various conditions (an introductory review)

[259] **COUNCIL FOR TOBACCO RESEARCH-USA**
Hatchell. The influence of genotype and sex on behavioral sensitivity to nicotine in mice

Vincek. Synthesis of 4,4-ditritio-(+)-nicotine: comparative binding and distribution studies with natural enantiomer

BRITISH-AMERICAN TOBACCO COMPANY, LTD. Unpublished
Creighton. Relative contributions of nicotine and carbon monoxide to human physiological response

Creighton. Further studies on the effect of nicotine on human physiological response

- plasma profiles of nicotine and its metabolites.[260]

Nicotine metabolism. The industry has investigated the metabolic fate of nicotine, including the metabolites (breakdown products) of nicotine.[261] Studies have also been done on the enzymatic systems involved in nicotine

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Isaac. The Absorption and Effects of Nicotine from Inhaled Tobacco Smoke

INDUSTRY SUPPORTED AMA/ERF STUDIES
Rosecrans. Brain area nicotine levels in male and female rats with different levels of spontaneous activity

Rosecrans. Brain area nicotine levels in male and female rats of two strains

OTHER
Cholerton. Sources of inter-individual variability in nicotine pharmacokinetics

Schmiterlow. Distribution of Nicotine in the Central Nervous System

OTHER, Literature Review
Edwards. Smoking, nicotine and electrocortical activity

[260] COUNCIL FOR TOBACCO RESEARCH-USA
Castro. Nicotine enzyme immunoassay

Haines. Radioimmunoassay of plasma nicotine in habituated and naive smokers

Monji. A Plasma nicotine pharmacokinetics in dogs after intravenous administration: Determination by radioimunassay

Rama. Distribution and Retention of nicotine and its major metabolite cotinine, in the rat as a function of time

AMERICAN TOBACCO COMPANY
Castro. Nicotine antibodies: comparison of ligand specificities of antibodies produced against two nicotine conjugates

R. J. REYNOLDS COMPANY
Davis. The determination of nicotine and cotinine in plasma

deBethizy. Absorption of nicotine from a cigarette that does not burn tobacco

Kyerematen. Pharmacokinetics of nicotine and 12 metabolites in the rat Application of a new radiometric high performance liquid chromatography assay

Kyerematen. Radiometric high performance liquid chromatographic assay for nicotine and twelve of its metabolites

BRITISH-AMERICAN TOBACCO COMPANY, LTD. Unpublished
Isaac. The absorption and effects of nicotine from inhaled tobacco smoke

TOBACCO RESEARCH COUNCIL LABS., U.K.
Armitage. Absorption and metabolism of nicotine from cigarettes

Armitage. Absorption of nicotine by man during cigar smoking [proceedings]

Armitage. Absorption of nicotine from small cigars

Armitage. The transfer of endogenous and exogenous radioisotopically labelled nicotine to mainstream cigarette smoke and its absorption into the blood of anaesthetized cats

Stepney. Behavioural regulation of nicotine intake in cigarette smokers presented with a 'shortened' cigarette [proceedings]

OTHER
Isaac. Cigarette smoking and plasma levels of nicotine

Isaac. Blood levels of nicotine and physiological effects after inhalation of tobacco smokeIsaac. Blood levels of nicotine and physiological effects after inhalation of tobacco smoke

Schievelbein. Nicotine Workshop

[261] COUNCIL FOR TOBACCO RESEARCH-U.S.A
Abood. Specific binding and metabolism of (-)- and (+)-[3H]-nicotine in isolated rat hepatocytes and hepatocyte membranes

Hibberd. Nicotine delta 1' (5)' iminium ion: a reactive intermediate in nicotine metabolism

Vincek. Synthesis of 4,4-ditritio-(+)-nicotine: comparative binding and distribution studies with natural enantiomer

AMERICAN TOBACCO COMPANY
Bowman. Studies on the metabolism of (-)-cotinine in the human

Bowman. Disposition and fate of (-)-cotinine-H3 in the mouse

Hucker. Studies on the metabolism of nornicotine in the dog

Larson. Studies on the fate of nicotine in the body III: On the pharmacology of some methylated and demethylated derivatives of nicotine

Larson. Studies on the fate of nicotine in the body IV: Observations on the chemical structure of an end product of nicotine metabolism

McKennis. Gamma-(3-pyridyl)-gamma-methylaminobutyric acid as a urinary metabolite of nicotine

McKennis. The excretion and metabolism of nicotine

McKennis. Mammalian degradation of (-)-nicotine to 3-pyridylacetic acid and other compounds

McKennis. Demethylation in the metabolism of (-)-nicotine

McKennis. Metabolic release of methyl groups from a series of N-methylpyridinium compounds

McKennis. Metabolism of nicotine to (+)-gamma-(3-pyridyl)-gamma- methylaminobutyric acid

McKennis. Demethylation of cotinine in vivo

McKennis. Metabolites of nicotine and a synthesis of nornicotine

metabolism.[262] Industry-supported research shows that smokers metabolize nicotine faster than non-smokers because one or more of the substances in cigarette smoke increases the production of the enzymes that metabolize nicotine.[263] Industry-funded studies have also shown that there may be gender differences in the metabolism of nicotine.[264]

Nicotine pharmacodynamics. The tobacco industry has studied a wide range of factors related to the pharmacodynamics of nicotine and nicotine delivery systems. (Pharmacodynamics is the study of a drug's effects on the body over time. A pharmacodynamic study would involve, for example, administering a drug and then evaluating its behavioral and physiological effects over time.) The industry has funded research on:

- factors affecting the onset and duration of nicotine's physiological effects on the body;[265]

McKennis. Demethylation in the metabolism of (-)-nicotine in vivo

McKennis. N-methylation of nicotine and cotinine in vivo

McKennis. The Metabolic Formation of Gamma-(3-Pyridyl)-Gamma- Hydroxybutyric Acid and Its Possible Intermediary Role in the Mammalian Metabolism of Nicotine

McKennis. The isolation and structure of a ketoamide formed in the metabolism of nicotine

Meacham. Additional routes in the metabolism of nicotine to 3-pyridylacetate

Miller. Observations on the metabolism of nicotine by tissue slices

Owen. Studies on the fate of nicotine in the animal body VIII: Observations on the nubmer and chemical nature of nicotine metabolites in the dog and cat

Schwartz. Studies on the degradation of the pyrrolidine ring of (-)-nicotine in vivo

Schwartz. Mammalian degradation of (-)-demethylcotinine

R. J. REYNOLDS COMPANY
Caldwell. Characterization of the glucuronide conjugate of cotinine: a previously unidentified major metabolite of nicotine in smokers' urine

Kyerematen. Disposition of nicotine and eight metabolites in smokers and nonsmokers: Identification in smokers of two metabolites that are longer lived than cotinine

TOBACCO RESEARCH COUNCIL LABS., U.K.
Jenner. Factors affecting the in vitro metabolism of R-(+)- and S-(-)-nicotine by guinea-pig liver preparations

Jenner. Species variation in the metabolism of R-(+)- and S-(-)-nicotine by alpha-C- and N-oxidation in vitro

OTHER
Fuxe. On the action of nicotine and cotinine on central 5-hydroxytryptamine

[262] **COUNCIL FOR TOBACCO RESEARCH-U.S.A**
Hibberd. Enzymology of the metabolic pathway from nicotine to cotinine, in vitro

Wilson. Nicotine-like actions of cis-metanicotine and trans-metanicotine

R. J. REYNOLDS COMPANY
Hammond. Metabolism of nicotine by rat liver cytochromes P-450: Assessment utilizing monclonal antibodies to nicotine and cotinine

[263] **COUNCIL FOR TOBACCO RESEARCH-U.S.A**
Hatchell. The influence of genotype and sex on behavioral sensitivity to nicotine in mice

Jusko. Role of tobacco smoking in pharmacokinetics

TOBACCO RESEARCH COUNCIL LABS., U.K.
Beckett. The effect of smoking on nicotine metabolism in vivo in man

[264] **COUNCIL FOR TOBACCO RESEARCH-U.S.A**
Jusko. Role of tobacco smoking in pharmacokinetics

TOBACCO RESEARCH COUNCIL LABS., U.K.
Beckett. The effect of smoking on nicotine metabolism in vivo in man

OTHER
Cohen. Monograph on the Pharmacology and Toxicology of Nicotine and its Role in Tobacco Smoking

[265] **COUNCIL FOR TOBACCO RESEARCH-USA**
Domino. Electroencephalographic and behavioral arousal effects of small doses of nicotine: A neuropsychopharmacological study

Hoff. Neurophysiological aspects of the action of nicotine

Lapin. Dopamine-like action of nicotine: lack of tolerance and reverse tolerance

Stitzer. Effects of nicotine on fixed-interval behavior and their modification by cholinergic antagonists

TOBACCO RESEARCH COUNCIL LABS., U.K.
Armitage. Absorption of nicotine in cigarette and cigar smoke through the oral mucosa

- the relationship of nicotine's physiological effects on the body to nicotine blood levels;[266] and
- physiological effects of nicotine on the brain and their time-course.[267]

3. Industry Research Establishes That Nicotine Produces Pharmacological Effects Similar to Those of Other Addictive Drugs

The tobacco industry has conducted or sponsored studies which demonstrate that nicotine produces pharmacological effects similar to those of other addictive substances. See FINDINGS § I.B., supra, for a discussion of the properties of addictive substances. Indeed, a number of industry-funded studies state that

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COUNCIL FOR TOBACCO RESEARCH-USA, Literature Reviews
Larson. Tobacco -- Experimental and Clinical Studies -- A Comprehensive Account of the World Literature -- Supplement I

Larson. Tobacco -- Experimental and Clinical Studies -- A Comprehensive Account of the World Literature -- Supplement II

Larson. Tobacco -- Experimental and Clinical Studies -- A Comprehensive Account of the World Literature --Supplement III

OTHER
Battig. Smoke yield of cigarettes and puffing behavior in men and women

Nordberg. Pharmacodynamic effects of nicotine and acetylcholine biosynthesis in mouse brain

[266] **COUNCIL FOR TOBACCO RESEARCH-U.S.A**
Hatchell. The influence of genotype and sex on behavioral sensitivity to nicotine in mice

Westfall. Influence of nicotine on catecholamine metabolism in the rat

R.J. REYNOLDS COMPANY
Pritchard. Flexible effects of quantified cigarette-smoke delivery on EEG dimensional complexity

BRITISH-AMERICAN TOBACCO COMPANY, LTD. Unpublished
Isaac. The absorption and effects of nicotine from inhaled tobacco smoke

OTHER
Isaac. Blood levels of nicotine and physiological effects after inhalation of tobacco smoke

[267] **COUNCIL FOR TOBACCO RESEARCH-U.S.A**
Abood. Comparison of the binding of optically pure (-)- and (+)-[3H]nicotine to rat brain membranes

Andersson. Effects of withdrawal from chronic exposure to cigarette smoke on hypothalamic and preoptic catecholamine nerve terminal systems and on the secretion of pituitary hormones in the male

Andersson. Effects of acute intermittent exposure to cigarette smoke on catecholamine levels and turnover in various types of hypothalamic DA and NA nerve terminal systems as well as on the secretion of adenohypophyseal hormones and corticosterone

Bhagat. Influence of chronic administration of nicotine on the turnover and metabolism of noradrenaline in the rat brain

Fuxe. Increases in dopamine utilization in certain limbic dopamine terminal populations after a short period of intermittent exposure of male rats to cigarette smoke

Fuxe. Effects of Nicotine and exposure to cigarette smoke on discrete dopamine and noradrenaline nerve terminal systems of the telencephalon and diencephalon of the rat: Relationship to reward mechanisms and neuroendocrine functions and distribution of nicotinic binding sites in brain

Tung. Peripheral induction of burst firing in locus coeruleus neurons by nicotine mediated via excitatory amino acids

Wong. Pharmacology of nicotinic receptor-mediated inhibition in rat dorsolateral septal neurones

Yamamoto. Nicotine-induced EEG and behavioral arousal

R.J. REYNOLDS COMPANY
Byrd. Evidence for urinary excretion of glucuronide conjugates of nicotine, cotinine, and trans-3'-hydroxycotinine in smokers

INDUSTRY SUPPORTED SYMPOSIA
Binnie. The effect of cigarette smoking on the contingent negative variation (CNV) and eye movement

INDUSTRY SUPPORTED AMA/ERF STUDIES
Hirschhorn. Studies on the time course and the effect of cholinergic and adrenergic receptor blockers on the stimulus effect of nicotine

Rosecrans. Brain area nicotine levels in male and female rats with different levels of spontaneous activity

TOBACCO RESEARCH COUNCIL LABS., U.K.
Armitage. The effects of nicotine on the electrocorticogram and spontaneous release of acetylcholine from the cerebral cortex of the cat

Wesnes. Smoking, nicotine and human performance

OTHER
Fuxe. On the action of nicotine and cotinine on central 5-hydroxytryptamine neurons

Hasenfratz. Development of central and peripheral smoking effects over time

Hasenfratz. Can smoking increase attention in rapid information processing during noise? Electrocortical, physiological and behavioral effects

Perez de la Mora. Neurochemical effects of nicotine on glutamate and GABA mechanisms in the rat brain

OTHER, Literature Review
Edwards. Smoking, nicotine and electrocortical activity

nicotine is an addictive/dependence-producing drug.[268]

Nicotine psychoactivity and discrimination studies. Industry studies have shown that nicotine is psychoactive and produces clearly discriminable stimulus effects[269] in both animals and humans.[270]

Nicotine reinforcement/self-administration studies. The industry has examined nicotine's ability to serve as a positive reinforcer in self-administration studies involving rats and monkeys. For example, Philip Morris conducted studies in rats demonstrating that nicotine is self-administered by rats and has other hallmark properties of addictive susbstances.[271] The industry-supported research on monkeys led prominent drug addiction researchers Deneau and Inoki to conclude in a paper published in 1967 that nicotine "may be one of

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[268] COUNCIL FOR TOBACCO RESEARCH-U.S.A
Bosse. Age and addiction to smoking

Martin. Tobacco Smoking and Nicotine: A Neurobiological Approach

Rosecrans. Noncholinergic Mechanisms involved in the behavioral and stimulus effects of nicotine, and relationships to the process of nicotine dependence

Rosecrans. Nicotine as a discriminative stimulus: a neurobehavioral approach to studying central cholinergic mechanisms

Svensson. Effect of nicotine on dynamic function of brain catecholamine neurons

Tung. Peripheral induction of burst firing in locus coeruleus neurons by nicotine mediated via excitatory amino acids

Williams. Stability of a factor-analytic description of smoking behavior

TOBACCO RESEARCH COUNCIL LABS., U.K.
Hall. New evidence for a relationship between tobacco smoking, nicotine dependence, and stress

OTHER
Andersson. Effects of acute central and peripheral administration of nicotine on ascending dopamine pathways in the male rat brain. Evidence for nicotine-induced increases of dopamine turnover in various telencephalic dopamine nerve terminal systems

Nisell. Systemic nicotine-induced dopamine release in the rat nucleus accumbens is regulated by nicotinic receptors in the ventral tegmental area

[269] These effects are evaluated in animals using drug discrimination techniques which enable direct comparisons of the effects of different drugs. Such studies evaluate whether an animal experiences a psychoactive effect from a drug and facilitate comparisons of the effect of the study drug with the effect of other psychoactive drugs. Industry-funded studies have shown that animals can distinguish (discriminate) nicotine from other drugs or a placebo, and can communicate their identification of nicotine (as distinct from other drugs) to the investigator by pressing a bar or providing other behavioral signals. These studies also provide information on the similarity of nicotine's effects to effects of other dependence-producing drugs, including the degree to which nicotine mimics the psychoactive effects of those other drugs. *See* p. 95.

[270] INDUSTRY SUPPORTED AMA/ERF STUDIES
Hirschhorn. Studies on the time course and the effect of cholinergic and adrenergic receptor blockers on the stimulus effect of nicotine

Schechter. Behavioral evidence for two types of cholinergic receptors in the C.N.S.

Schechter. Behavioral tolerance to an effect of nicotine in the rat

Schechter. Effect of mecamylamine on discrimination between nicotine- and arecoline- produced cues

Schechter. Nicotine as a discriminative cue in rats: inability of related drugs to produce a nicotine-like cueing effect

Schechter. Nicotine as a discriminative stimulus in rats depleted of norepinephrine or 5-hydroxytryptamine

Schechter. C.N.S. effect of nicotine as the discriminative stimulus for the rat in a T-maze

COUNCIL FOR TOBACCO RESEARCH-U.S.A
Chance. A comparison of nicotine and structurally related compounds as discriminative stimuli

Rosecrans. Nicotine as a discriminative stimulus: a neurobehavioral approach to studying central cholinergic mechanisms

PHILIP MORRIS TOBACCO COMPANY
Kallman. Nicotine as a discriminative stimulus in human subjects

TOBACCO RESEARCH COUNCIL LABS., U.K.
Morrison. Nicotine injections as the conditioned stimulus in discrimination learning

[271] PHILIP MORRIS TOBACCO COMPANY, Unpublished
DeNoble. Manuscript: Nicotine as a Positive Reinforcer for Rats: Effects of Infusion Dose and Fixed Ratio Size

See also pp. 278-79, *infra.*

INDUSTRY SUPPORTED AMA/ERF STUDIES
Deneau. Nicotine self-administration in monkeys

the substances in tobacco smoke which is responsible for man's use of tobacco."[272] The industry has also funded studies demonstrating that nicotine could enhance the rewarding effects of electrical brain stimulation.[273] A book resulting from The International Smoking Behaviour Conference held at Chelwood Vachery, Sussex, England, in 1978, which was edited by a senior scientist at British-American Tobacco, included a "Conference Overview" stating: "At this stage, we hypothesize that nicotine (possible [sic] interacting with tar) is the main reinforcing agent in cigarettes . . . "[274] Moreover, as noted earlier, the industry has conducted studies showing that nicotine is active in the same dopaminergic pathways that modulate cocaine's effects. These studies are relevant to understanding how nicotine causes addiction.

Tolerance to nicotine. Tolerance to the physiological and behavioral effects of nicotine has been thoroughly studied by the tobacco industry and has been demonstrated to occur in animals as a result of nicotine use.[275]

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[272] **INDUSTRY SUPPORTED AMA/ERF STUDIES**
Deneau. Nicotine self-administration in monkeys

[273] **COUNCIL FOR TOBACCO RESEARCH-U.S.A.**
Olds. Comparision of muscarinic and nicotinic cholinergic agonists on self-stimulation behavior

Pradan. Effects of nicotine on self-stimulation in rats

[274] **INDUSTRY SUPPORTED SYMPOSIA**
Jarvik. Smoking Behaviour -- Physiological and psychological influences. 31. Conference overview

[275] **COUNCIL FOR TOBACCO RESEARCH-U.S.A**
Abood. Acute and chronic effects of nicotine in rats and evidence for a non-cholinergic site of action

Abood. Behavioral and biochemical studies in rats after chronic exposure to nicotine

Andersson. Effects of withdrawal from chronic exposure to cigarette smoke on hypothalamic and preoptic catecholamine nerve terminal systems and on the secretion of pituitary hormones in the male

Cronan. Effects of chronically administered nicotine and saline on motor activity in rats

Domino. Tolerance to the effects of daily nicotine on rat bar pressing behavior for water reinforcement

Fuxe. Effects of nicotine and exposure to cigarette smoke on discrete dopamine and noradrenaline nerve terminal systems of the telencephalon and diencephalon of the rat: Relationship to reward mechanisms and neuroendocrine functions and distribution of nicotinic binding sites in brain

Lapin. Dopamine-like action of nicotine: lack of tolerance and reverse tolerance

Nelsen. Improvement of performance on an attention task with chronic nicotine treatment in rats

Rosecrans. Noncholinergic Mechanisms involved in the behavioral and stimulus effects of nicotine, and relationships to the process of nicotine dependence

Stitzer. Effects of nicotine on fixed-interval behavior and their modification by cholinergic antagonists

Wenzel. Studies on the acute and chronic depressor actions of nicotine in the rat

Westfall. Studies on the mechanism of tolerance to nicotine-induced elevations of urinary catecholamines

R. J. REYNOLDS COMPANY
Bjercke. Anti-idiotypic antibody probes of neuronal nicotinic receptors

Collins. Modulation of nicotine receptors by chronic exposure to nicotinic agonists and antagonists

Marks. Downregulation of nicotinic receptor function after chronic nicotine infusion

PHILIP MORRIS TOBACCO COMPANY, Unpublished
DeNoble. Manuscript: Development of behavioral tolerance following chronic nicotine administration.

INDUSTRY SUPPORTED AMA/ERF STUDIES
Schechter. Behavioral tolerance to an effect of nicotine in the rat

TOBACCO RESEARCH COUNCIL LABS., U.K.
Morrison. The occurrence of tolerance to a central depressant effect of nicotine

OTHER
Larsson. Subchronic treatment of rats with nicotine: effects on tolerance and on [3H]acetylcholine and [3H]nicotine binding in the brain

Nordberg. Effect of acute and subchronic nicotine treatment on cortical acetylcholine release and on nicotinic receptors in rats and guinea-pigs

Nordberg. Effect of long-term nicotine treatment on [3H]nicotine binding sites in the rats brain

Nicotine's withdrawal effects. Scientists funded by the tobacco industry have conducted research on various aspects of withdrawal, including potential neurochemical mechanisms[276] and the effects of withdrawal on performance.[277] Symptoms of withdrawal may include craving, irritability, nervousness, tension, emotional strain, depression, inability to concentrate, sleep disturbance, sweating, gastrointestinal changes, drop in blood pressure and pulse rate, impaired performance, and changes in the electroencephalogram.[278]

The industry has also funded studies showing that tobacco users report "craving" for tobacco.[279]

Continued use of tobacco despite attempts to quit. As described in § II.C.4., infra, the tobacco industry has conducted a number of studies documenting the large percentage of tobacco users who have attempted to quit using tobacco and the very small percentage who have succeeded.

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[276] **COUNCIL FOR TOBACCO RESEARCH-U.S.A**
Andersson. Effects of withdrawal from chronic exposure to cigarette smoke on hypothalamic and preoptic catecholamine nerve terminal systems and on the secretion of pituitary hormones in the male

Fuxe. Effects of Nicotine and exposure to cigarette smoke on discrete dopamine and noradrenaline nerve terminal systems of the telencephalon and diencephalon of the rat: Relationship to reward mechanisms and neuroendocrine functions and distribution of nicotinic binding sites in brain

Rosecrans. Noncholinergic Mechanisms involved in the behavioral and stimulus effects of nicotine, and relationships to the process of nicotine dependence

COUNCIL FOR TOBACCO RESEARCH-U.S.A., Literature Reviews
Larson. Tobacco -- Experimental and Clinical Studies -- A Comprehensive Account of the World Literature -- Supplement II

Larson. Tobacco -- Experimental and Clinical Studies -- A Comprehensive Account of the World Literature --Supplement III

AMERICAN TOBACCO COMPANY
Finnegan. The role of nicotine in the cigarette habit

[277] **COUNCIL FOR TOBACCO RESEARCH-U.S.A**
Heimstra. The effects of deprivation of cigarette smoking on psychomotor performance

Heimstra. Effects of smoking upon sustained performance in a simulated driving task

COUNCIL FOR TOBACCO RESEARCH-U.S.A., Literature Reviews
Fuxe. Neuroendocrine actions of nicotine and of exposure to cigarette smoke: medical implications

Larson. Tobacco -- Experimental and Clinical Studies -- A Comprehensive Account of the World Literature --Supplement III

OTHER
Hasenfratz. Psychophysiological reactions during active and passive stress coping following smoking cessation

[278] **COUNCIL FOR TOBACCO RESEARCH-U.S.A., Literature Reviews**
Larson. Tobacco -- Experimental and Clinical Studies -- A Comprehensive Account of the World Literature -- Supplement II

Larson. Tobacco -- Experimental and Clinical Studies -- A Comprehensive Account of the World Literature --Supplement III

AMERICAN TOBACCO COMPANY
Finnegan. The role of nicotine in the cigarette habit

[279] **R. J. REYNOLDS COMPANY**
Robinson. The meaning of addiction: reply to West

OTHER
Hasenfratz. Development of central and peripheral smoking effects over time

Hasenfratz. Post-lunch smoking for pleasure seeking or arousal maintenance?

C. INDUSTRY RESEARCH ON THE CONSUMER'S NEED FOR AN ADEQUATE DOSE OF NICOTINE

1. Industry Research on Importance of Supplying Sufficient Nicotine to Provide Consumer Acceptance and "Satisfaction"

The industry has conducted extensive research establishing that smokers require a certain level of nicotine from their cigarettes and that tobacco "satisfaction" is attributable to nicotine's systemic effects after absorption, rather than to its immediate sensory effects in the mouth, nose, and throat.[280]

In the mid 1970's, BATCO Group Research & Development conducted Project Wheat, a study whose purpose was to identify the different motivations for smoking and correlate those motivations with what BATCO characterized as a smoker's "Inner Need level."[281] The researchers established smokers' "Inner Need level" by identifying the extent to which they smoked to relieve stress, to aid concentration, and as a food substitute to avoid weight gain.[282] In other words, a smoker's "Inner Need" was defined by the extent to which the smoker used cigarettes for the drug effects of nicotine. (See description of the effects of nicotine on mood and weight in FINDINGS § I.D., supra.) The researchers hypothesized that the "Inner Need

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[280] BATCO Group Research & Development Centre. Research Conference. Southampton, England. September, 1984. Page 1. Proposed Revisions for 1985-87:

> *Specific attention will be focussed on nicotine to identify its contribution to product attributes, particularly acceptability and satisfaction. A range of de-nicotinised tobacco blends, supplemented with varying levels of nicotine, will be prepared. These will be used in studies aimed at assessing the specific sensory properties of nicotine and the relationship between tar and nicotine in terms of product acceptability. The studies will provide an initial opportunity to separate immediate product acceptability from longer-term satisfaction.*

[281] *See* Project Wheat - Part 1, note 204, *supra,* at p. 1; Project Wheat - Part 2, note 204, *supra,* at p. 1.

[282] *See* Project Wheat - Part 1, note 204, *supra,* at pp. 5, 10-11, 16-25.

level" would correlate with the smoker's preferred nicotine delivery, and that smokers with higher "Inner Need" would prefer cigarettes that delivered higher nicotine levels.

Project Wheat was intended to help BATCO develop cigarettes that were more acceptable to consumers.[283] The Project Wheat researchers emphasized the importance of nicotine delivery over all other product features (including taste) in achieving an acceptable and satisfying cigarette:

> *In considering which product features are important in terms of consumer acceptance, the nicotine delivery is one of the more obvious candidates. Others include the taste and flavour characteristics of the smoke, physical features such as draw resistance and rate of burn, and the general uniformity of the product, to name but a few. The importance of nicotine hardly needs to be stressed, as it is so widely recognised.*[284] [Emphasis added.]

The researchers found that "Inner Need" correlated positively with daily cigarette consumption, depth of inhalation, and anticipated difficulty in giving up smoking; i.e., a higher "Inner Need" smoker would smoke more cigarettes, inhale more deeply, and anticipate greater difficulty in quitting smoking than a lower "Inner Need" smoker.[285] The researchers concluded that "Inner Need" defined a requirement for nicotine by the smoker.[286]

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[283] *See* Project Wheat - Part 1, note 204 *supra,* at p.1.

[284] *See* Project Wheat - Part 1, note 204 *supra,* at p. 3.

[285] *Id.* at p. 2.

[286] BATCO Group R&D *Conference on Smoking Behavior.* October 11-12, 1976, at p. BW-W2-02295.

The Project Wheat researchers also found that smokers of low nicotine delivery cigarettes derive less satisfaction from their cigarettes than smokers of medium or high nicotine cigarettes.

> *Compared with the other two categories of smoker [medium and high], those respondents who smoke low nicotine cigarettes (less than 1.0 mg per cigarette) see their brand as milder, smoother, less satisfying and with not quite such a good taste, comments which are of course perfectly logical.*

Project Wheat - Part 2, note 204, *supra,* at p. 10.

Tobacco industry documents show that smoker "satisfaction" is one of the key attributes of consumer acceptance of tobacco products. These documents also make clear that "satisfaction" is a tobacco industry euphemism that refers to the pharmacological response to nicotine that smokers seek to obtain from smoking.[287] A BATCO scientist, in a 1969 presentation describing the research activities of BATCO Group Research & Development, stated that:

> *The presence of nicotine is the reason why the tobacco plant was singled out from all other plants for consumption in this rather unusual way.*

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[287] Wood DJ. BATCO Group Research & Development. "Aspects of the R&DE Function. Notes for a talk given at Chelwood. September, 1969." (The document bears the date July 20, 1970). Page 7.

See also:

Proceedings of BATCO Group R&D Smoking Behaviour-Marketing Conference, Session I. July 9-12, 1984. Session I discusses nicotine's whole body dose and its relationship to smoker satisfaction. *See*, e.g., p. BW-W2-03242: nicotine underlies smoking maintenance "and as a consequence probably provides the basis of smoking satisfaction"; at p. 03243: nicotine's "whole body response [is] associated with satisfaction." Session II discusses methods for assessing smoker response to changing deliveries:

> *German butt analysis [testing of cigarette butts to determine smokers' nicotine uptake] and switching experiments [exposing smokers to cigarettes with varying deliveries] were used to indicate the capacity of external studies [as opposed to laboratory measures of smokers' nicotine uptake] to indicate . . . measurement of smokers changing the way they smoke in order to satisfy their needs.*

Ferris, RP. Notes from the Proceedings of the Smoking Behaviour-Marketing Conference. July 9-12, 1984. Page 21.

Imperial Tobacco. Matinee Marketing Strategy. 1971. Page 11. "A cigarette that delivers physiological satisfaction, yet is low in tar and nicotine, must surely be a major objective..."

BATCO Structured Creativity Conference. Southampton, England. June 25-28, 1984. The purpose of this conference was "to stimulate genuinely innovative product-based project ideas." Moist snuff was proposed as an alternative to cigarettes so as "[t]o capitalise on the potential downtrend of the smoking habit as the only means to achieve nicotine satisfaction by participating in a parallel product market free of social/health concerns and with attractive profitability." [Emphasis added.]

BATCO Group R & D. Research Conference. Rio de Janeiro, Brazil. August 22-26, 1983, at p. BW-W2-01838.

BATCO Group R & D. Nicotine Conference Outline. Southampton, England. June 6-8, 1984, at p. BW-W2-01977.

Nicotine has well documented pharmacological action. It is claimed to have a dual effect, acting both as a stimulant and a tranquilliser. It is believed to be responsible for the "satisfaction" of smoking, using this term in the physiological rather than the psychological sense.[288]

The proceedings to the 1983 BATCO Group R&D Research Conference in Rio de Janeiro state that:

The basic assumption is that nicotine, which is almost certainly the key smoke component for satisfaction, is fully released to the body system before exhalation takes place. [Emphasis added].[289]

A 1984 BATCO Nicotine Conference similarly concluded that:

Intuitively it is felt that "satisfaction" must be related to nicotine. Many people believe it [is] a "whole body response" and involves the action of nicotine in the brain.[290]

An RJR-MacDonald Marketing Summary Report from 1983 concludes that the primary reason people smoke "is probably the physiological satisfaction provided by the nicotine level of the product."[291]

The term "satisfaction" is also used by the smokeless tobacco industry to refer to the physiological effects of nicotine on the user. The senior vice president for marketing of the U.S. Tobacco Co. wrote in a memo on new product development:

Flavorwise we should try for innovation, taste and strength, nicotine should be medium . . . Virtually all tobacco usage is based upon nicotine, "the kick."

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[288] *See* Wood, note 287, *supra*, at p. 7.

[289] *See* BATCO Group R & D Research Conference, Rio de Janeiro, 1983, note 287, *supra*, at p. 10.

[290] *See* BATCO Conference Outline, 1984, note 287, *supra*, at p. BW-W2-01977.

[291] *RJR-MacDonald v. Canada*, 5.3 TPLR 4.26.

satisfaction. [Emphasis added.][292]

These documents show that tobacco companies know that tobacco "satisfaction" is provided by nicotine's pharmacological effects on the brain and that the industry strives to offer products that meet this need.

[292] Deposition of Per Erik Lindqvist, *Marsee v. U.S. Tobacco*, Civil Action No. 84-2777R (W.D. Ok. 1986). Transcript of Jury Trial Proceedings at p.1662. In: 1.7 TPLR 3.216.

2. Industry Research to Determine the Minimum and Maximum "Dose" of Nicotine Required by Consumers of Tobacco

The tobacco industry has focused extensive research efforts on methods to assay systemic nicotine absorption so that it may estimate nicotine doses obtained and required by smokers.[293] Tobacco company documents reveal that the primary purposes of these efforts are to better understand the relationship between nicotine dose and nicotine's pharmacological effects in smokers, and to establish the level of nicotine that must be provided in tobacco to produce these effects. Better knowledge of nicotine's dose-response effect in smokers results in a better understanding of how smokers respond to cigarettes with varying nicotine deliveries and how different doses of nicotine may affect smoker satisfaction.

As early as 1970, the tobacco industry had investigated and attempted to determine the

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[293] *See e.g.*:
BATCO. *Fate of Nicotine in the Body.* 1963.

BATCO R&D. *Relation Between 'Extractable Nicotine' Content of Smoke and Panel Response.* March 17, 1967.

BATCO R&D. *Nicotine in Smoke and Human Physiological Response.* March 26, 1970.

BATCO. *Relative Contributions of Nicotine and Carbon Monoxide to Human Physiological Response.* November 15, 1971.

BATCO Group R&D *Further Studies of the Effect of Nicotine on Human Physiological Response.* June 5, 1973.

Proceedings of the BATCO Group R&D Smoking Behaviour-Marketing Conference. Session I. July 9-12, 1984. Page 16 (slides).

See Ayres, note 172, *supra.*

BATCO Group R&D *Nicotine Studies: A Second Report. Estimation of Whole Body Nicotine Dose by Urinary Nicotine and Cotinine Measurement.* March 31, 1981. Page 3.

Proceedings of the BATCO Smoking Behaviour-Marketing Conference, Session I (1984):21, slide at p. BW-W2-03243; *Session II* (1984):21, slide at p. BW-W2-02406.

minimum level of nicotine necessary for consumer acceptance. At a BATCO R&D Conference held that year, the conferees agreed that:

> *Nicotine is important, and there is probably a minimum level necessary for consumer acceptance in any given market.*[294]

A 1972 Philip Morris document from a Council for Tobacco Research conference addressing why people smoke reveals the basis of the industry's concern about maintaining nicotine levels above a defined minimum:

> *Despite many low nicotine brand entries into the marketplace, none of them have captured a substantial segment of the market. In fact, critics of the industry would do well to reflect upon the indifference of the consumer to the industry's efforts to sell low-delivery brands. 94% of the cigarettes sold in the U.S. deliver more than 1 mg of nicotine. 98.5% deliver more than 0.9 mg. The physiological response to nicotine can readily be elicited by cigarettes delivering in the range of 1 mg of nicotine.* [Emphasis added.][295]

Similarly, the 1984 BATCO Group R & D Nicotine Conference concluded:

> *Cigarettes which have a delivery of less than 0.7 mg of nicotine per cigarette as measured on a smoking machine, do not achieve large volume sales.*[296]

In Project Wheat, discussed in § II.C.1., supra, a 0.7 mg nicotine test cigarette was found to be unacceptable by smokers regardless of the smokers' relative nicotine requirements; the low-dose product was rejected by smokers with both high and low nicotine requirements.[297]

An internal Philip Morris document from 1978, detailing plans to study cigarettes wit

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[294] BATCO Group R&D *Summary Conclusions: Group Research Conference.* St Adele, Canada. September 11, 1970. Page 1.

[295] *See* Dunn, note 133, *supra,* at p. 4.

[296] BATCO Conference Outline, 1984, note 287 *supra,* at p. BW-W2-01977.

[297] *See* Project Wheat - Part 2, note 204, *supra,* at p. 47.

different levels of nicotine at a given tar level, shows that Philip Morris, too, conducted studies to find the minimum level of nicotine delivery necessary to satisfy smokers' need for nicotine:

> *Question 4. Tar delivery delivery being the same, what are the behavioral consequences of smoking low nicotine rather than high nicotine cigarettes?*
> *This question will be answered by conducting a series of shift studies using cigarettes of similar low tar but differential nicotine deliveries. The low nicotine delivery will ensure that the total nicotine in the system remains at or near the nicotine need threshold, thus maximizing the proportion of the day's cigarette consumption which is smoked out of need . . .*
> *The results may shed light on the manner by which nicotine control is achieved.*[297a] [Emphasis added.]

Demonstrating the industry's continuing interest in determining the minimum dose of nicotine that must be contained in a cigarette to provide satisfaction, the BATCO "Group R&D Research Programme, 1984: Proposed revisions for 1985-87," states that studies would be done by the industry

> *to establish the minimum dose of smoke nicotine that can provide pharmacological satisfaction for the smoker.* [Emphasis added.][298]

One key to identifying the minimum and maximum doses of nicotine was the development of a method to accurately measure nicotine in the human body. A 1976 Council for Tobacco Research Annual Report identifies a need for better methods to measure nicotine levels in human smokers:

> *. . .an expansion of information on the actual ranges or durations of plasma nicotine levels attained by human smokers (and users of other forms of tobacco) under actual conditions of life should be attainable . . . Sensitive, specific and rapid assays for plasma nicotine and its major metabolites have*

[297a] Memorandum to T.S. Osdene from W.L. Dunn. Plans and Objectives - 1979. December 6, 1978. *In* Cong Rec. H7670 (daily ed. July 25, 1995).

[298] *See* BATCO, note 280, *supra,* at p. 2.

long been needed.[299]

Another series of studies conducted by Philip Morris was designed to discover the relationship between the dose of nicotine provided by a cigarette, the level of nicotine in the bloodstream following that cigarette, and the length of time before the nicotine in the bloodstream fell to the point that the smoker experienced the urge for another cigarette. This required Philip Morris to develop an assay for nicotine and saliva and correlate salivary nicotine with blood nicotine:

> *Our theorizing on the role of nicotine suggests that cigarettes will be smoked whenever body nicotine content drops below a certain (unknown) level . . . .*
>
> *We are engaged in systematic investigation of the changes in salivary nicotine content as a function of the time since smoking and magnitude of intake . . . .*
>
> *Assuming that salivary nicotine concentrations will reflect blood nicotine concentrations, we can then proceed to a fourth stage in the research, relating the easily obtained salivary concentrations to the urge to smoke.*[299a] [Emphasis added.]

A 1980 BATCO Group R&D study report, "Method for Cotinine and Nicotine in Blood and Urine," describes an improved analytical method for the simultaneous measurement of nicotine and cotinine (nicotine's major metabolite in man) in samples of blood and urine.[300]

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[299] Report of the Council for Tobacco Research - U.S.A., Inc. Annual Report 1976. Page 12.

[299a] Memorandum to T.S. Osdene from W.L. Dunn. Plans and Objectives - 1980. January 7, 1980. *In* Cong Rec. H7672 (daily ed. July 25, 1995).

[300] Read GA, Anderson IGM. BATCO Group R&D *Method for Nicotine and Cotinine in Blood and Urine.* Report No. RD 1737-C. May 21, 1980. Page 12 (established and validated an assay for nicotine and cotinine in blood and urine that is sufficiently sensitive to determine changes in ". . . plasma levels of nicotine achieved in response to varying concentrations of or different dose levels of nicotine").

See also New Cigarette Prototypes that Heat Instead of Burn Tobacco. Winston-Salem, NC: R.J. Reynolds Tobacco Co. 1988:457-557. Comparative study of humans smoking the NEW CIGARETTE and a Reference Cigarette. (Compared nicotine pharmacokinetics in smokers smoking the New (heated tobacco) cigarette and a regular burning cigarette to determine whether the New cigarette provided a nicotine dose comparable to a regular burning cigarette. Researchers measured smokers' plasma and urine

The method was developed to better study the systemic effects of nicotine and the extent to which those effects influence smoking behavior and smoker satisfaction. The report states:

> *In some instances, the pharmacological response of smokers to nicotine is believed to be responsible for an individual's smoking behaviour, providing the motivation for and the degree of satisfaction required by the smoker. [Emphasis added.]*[301]

> *Naturally, during any study of the biological effect of nicotine it is of paramount importance to accurately assess the dose of nicotine absorbed . . . [W]here the causal relationship between nicotine and individual biochemical, physiological or psychological responses are to be investigated, accurate information regarding nicotine dose is essential.* [Emphasis added.][302]

A 1981 BATCO Group R&D study developed a rat model to estimate "whole body nicotine dose" by measuring urinary nicotine and cotinine levels. The researchers concluded that the model would likely be a good predictor of nicotine dose in humans and, therefore, would aid in understanding the relationship between nicotine delivery and smokers' choice of particular brands:

> *These results strongly suggest that the whole body dose of nicotine can be predicted from urinary levels of nicotine and cotinine. The findings have immediate and obvious significance to both animal toxicity and human behavioural studies. They are particularly relevant to the development of an understanding of an individual smoker's daily nicotine requirement and the relationship between nicotine dose and smoking behaviour under conditions of brand switching/delivery modification.* [Emphasis added.][303]

A presentation at a 1983 BATCO Smoking Behavior Conference describes how to

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concentrations of nicotine to compare nicotine doses.)

[301] *See* Read, note 300, *supra,* at p. 2.

[302] *Id.* at pp. 2-3.

[303] BATCO Group R&D *Nicotine Studies: A Second Report. Estimation of Whole Body Nicotine Dose by Urinary Nicotine and Cotinine Measurement.* March 3, 1981, at pp. 9-10.

design and execute a study of plasma cotinine as a function of cigarette nicotine delivery.[304] It establishes that there is a linear relationship between plasma cotinine and nicotine delivery. A session on "Nicotine Dose Estimation" at BATCO's 1984 Smoking Behaviour-Marketing Conference was intended "to review the current status of plasma/urinary measures estimates [sic] of nicotine dose and to identify the significance of those measures for the smoker and product design." It was concluded that:

> *[u]nder appropriate conditions plasma nicotine and cotinine measures can be used to estimate daily nicotine intake.*[305]

Using assay methods such as those discussed above, tobacco companies have discovered that smokers obtain a fairly consistent dose of nicotine from tobacco. Moreover, tobacco companies are aware that smokers obtain this dose to maintain a desired blood level of nicotine throughout the day, and that achieving this dose results in smoker satisfaction.[306] For example, following a presentation on the role of nicotine in smoking behavior at the 1976 BATCO Conference on Smoking Behavior, it was observed "that smokers may be people suffering from a nicotine disorder and needed a certain dose level per day."[307] The speaker agreed and referred to a Battelle study which found that the nicotine level of smokers remained constant during the day, dropped during the night, and was restored to near its

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[304] Deines WH. BATCO. *Smoking Behaviour Conference: Overview.* 1983. (Attended by eight B&W employees). Page BW-W2-03280.

[305] Proceedings of the BATCO Smoking Behaviour-Marketing Conference, Session I. July 9-12, 1984. Montreal, Canada. Slide at p. BW-W2-02641, "Nicotine Dose Estimation."

[306] Proceedings of the BATCO Smoking Behaviour-Marketing Conference, Session I. July 9-12, 1984. Slides at pp. BW-W2-03243, BW-W2-03236: "whole body response: associated with satisfaction . . . [whether] dose of nicotine is adequate or inadequate."

[307] Proceedings of the BATCO Group R&D Smoking Behaviour-Marketing Conference. (Mrs. A.K. Comer, speaker.) Discussion on paper No. 2. October 1976. Southampton, England. Page BW-W2-02150.

daytime constant level by the first cigarette of the day.[308] The conferees then speculated that there may be a maximum dose of nicotine and that after this dose is achieved smokers may use cigarettes for reasons other than obtaining nicotine:

> *A further question in this area was whether there is a maximum nicotine level in smokers and, when this has been achieved, does the smoker smoke for reasons other than to obtain nicotine?*[309]

A paper presented at the 1977 BATCO International Smoking Behaviour Conference concluded that smokers adjust their smoking rate, depending on psychological factors and even diet, to maintain a certain body nicotine content.[310]

Relying on plasma nicotine/cotinine measurements, a 1984 BATCO Nicotine Conference concluded that:

> *[such] measurements can give reliable estimates of the nicotine uptake by groups of smokers, and with suitable precautions, by an individual smoker. Many smokers appear to obtain 12-14 mg of nicotine per day from their cigarettes.*[311]

A BATCO presentation from the 1984 BATCO Smoking Behaviour-Marketing Conference entitled "Current Status and Future Direction of Smoking Behavior Research" contains a discussion of whole body dose and whole body pharmacological properties of nicotine in relation to smoking satisfaction.[312] A chart accompanying the presentation plots a

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[308] *Id.* at p. BW-W2-02151.

[309] *Id.* at p. BW-W2-02151.

[310] BATCO International Smoking Behaviour Conference. Chelwood Vachery, England. 1977. Page 2.

[311] *See* BATCO Conference Outline, 1984, note 287, *supra,* at p. BW-W2-01977.

[312] Proceedings of the BATCO Smoking Behaviour-Marketing Conference, Session I. Montreal, Canada. July 9-12, 1984. Page BW-W2-03236.

24-hour nicotine blood level curve, with peaks representing the nicotine dose obtained from cigarettes smoked during the day. Each peak actually represents a series of smaller peaks that indicate the dose of nicotine delivered by each puff. Each puff is characterized as a "pulsed high concentration bolus dose of nicotine."[313]

The report states that among smokers there is broad consistency in the whole body nicotine doses obtained by different groups and types of smokers.[314] This is so despite the fact that smoking products have a wide range of nicotine deliveries and despite wide variations in smoking behavior, such as puff duration, puff intensity, puff volume, puff interval, and depth of inhalation. The report states that the fact that widely disparate smoking behavior nonetheless results in fairly consistent whole body nicotine doses (12-14 mg per day) across a broad range of smokers demonstrates that nicotine underlies smoking maintenance.[315] Smokers maintain a fairly consistent whole body dose or blood level and self-administer additional nicotine doses when total body nicotine dose declines due to metabolism of nicotine. Therefore, the report concludes, the dose of nicotine "probably provides the basis for smoking satisfaction"[316] as it restores the whole body dose to the desired level.

The smokeless tobacco industry has also investigated the dose of nicotine that is absorbed into the blood and bodies of smokeless tobacco users. Pharmacokinetic studies

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[313] *Id.* at p. BW-W2-03238.

[314] *Id.* at p. BW-W2-03241.

[315] *Id.* at p. BW-W2-03241-42.

[316] *Id.* at p. BW-W2-03242.

performed by the U.S. Tobacco Co. (UST) reveal that the researchers were interested in how much nicotine was absorbed into the body, how much was metabolized, and how fast nicotine and its metabolites were eliminated from the body. Documents admitted into evidence in a court case reveal that the company investigated the disposition profile of nicotine and its metabolite in both plasma and urine in naive and habituated users of tobacco snuff.[317] The study found no difference between these two populations. UST also performed a study to compare the pharmacokinetics of nicotine and its metabolites following administration of snuff and cigarettes.[318] According to a report of the study, the purpose of this research was to "delineate the similarities and differences in nicotine pharmacokinetics after acute and chronic use of smoked and smokeless tobacco products."[319]

The tobacco industry has also investigated the difference between minimum acceptable and optimum nicotine levels. Project Wheat was designed to test the assumption that the optimum level of nicotine might vary for different types of smokers. The study report concludes that the optimum nicotine delivery for U.K. male smokers is approximately 1.5 mg of nicotine. An earlier Imperial Tobacco study referenced in the Project Wheat report had similarly concluded that the optimum nicotine delivery for U.K. smokers was around 1.4 mg per cigarette and that stepwise reduction in nicotine delivery caused progressive rejection of

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[317] U.S. Tobacco Co. *Pharmacokinetics of Nicotine and its Major Metabolites in Naive and Habituated Snuff Takers*. Plaintiff's exhibit 3.27 from *Marsee v. U.S. Tobacco* (W.D. Ok. 1986) (Civil Action No. 84-2777R).

[318] U.S. Tobacco Co. *Results of Comparison of Routes of Nicotine Administration.* Plaintiffs exhibit 3.28 from *Marsee v. U.S. Tobacco*, note 317, *supra.*

[319] *Id.*

the 1.4-mg cigarette by consumers.[320]

These documents make clear that the industry is aware that tobacco products must deliver an adequate dose of nicotine, that there is a minimum dose below which the desired pharmacological effects of nicotine are not elicited, and that consumers will not accept a product that does not deliver an adequate dose of nicotine.[321]

[320] *See* Project Wheat - Part 2, note 204, *supra,* at p. BW-W2-01721-2.

[321] Although currently marketed low-delivery products may "yield" less than the amount of nicotine shown in these industry documents to be the minimum accepted dose, machine measured yields may underestimate the amount of nicotine smokers actually obtain from cigarettes. *See* FINDINGS § I.C. at p. 112.

3. Industry Research on How Consumers "Compensate" to Achieve an Adequate Dose of Nicotine

When smokers are given cigarettes with a lower nicotine yield (as measured by a smoking machine), than their regular brands, they often "compensate" by smoking the cigarette more intensely, e.g., by taking larger or more puffs, or by smoking more cigarettes.[322] Tobacco company documents reveal that the industry recognizes both that smokers compensate and that the purpose of compensating behavior is to allow smokers to obtain a dose of nicotine that satisfies their physiological need for nicotine.[323] The industry's

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[322] *See, e.g.:*

Guyatt AR, Kirkham AJ, Baldry AG, Dixon M, Cumming G. *How Does Puffing Behavior Alter During Smoking of a Single Cigarette?* Pharmacol. Biochem. Behav. 1989;33(1):189-195.

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.

Memorandum from P.N. Lee to H.R. Bentley. *Tar Reduction and Nicotine Compensation.* July 19, 1979. Attached to the memorandum is a document that reviewed the existing scientific literature on smoking compensation prepared by Lee for the UK's Tobacco Advisory Council, July 19, 1979. The author concluded, at page 4, that:

> *Taken together, the evidence above seems to indicate that a smoker, when switching to a brand with lower nicotine yield, will tend to 'compensate' mainly by altering inhalation patterns but partly perhaps by a small increase in consumption.*

[323] "Compensation" is acknowledged in the following documents, among others:

BATCO Group R&D Conference. *The Effect of Puff Volume on "Extractable Nicotine" and on the Retention of Nicotine in the Mouth.* Laboratory Report No. L.314-R. Southampton, England. August 21, 1969.

Creighton D, McGillivray LM. BATCO R&DE. *Relative Contributions of Nicotine and Carbon Monoxide to Human Physiological Response.* Report No. RD839-R. Southampton, England. November 15, 1971. Page 22.

Armitage AK. Some recent observations relating to the absorption of nicotine from tobacco smoke. In: Dunn WL, ed. *Smoking Behavior: Motives and Incentives.* Washington, DC: VH Winston & Sons; 1973:83:

> *The human smoker can and does adjust the dose of nicotine he takes into his mouth very subtly, by adjusting either the size of his puff or the rate at which he puffs (this was shown very clearly by the elegant experiments of Ashton and Watson [1970], to which*

study of compensation by smokers provides compelling evidence that the industry knows that its market is based on nicotine dependence and that tobacco products are nicotine delivery systems.

Tobacco company researchers have repeatedly recognized the phenomenon of compensation and acknowledge that it occurs because smokers are seeking a specific dose of

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Domino [this volume] referred); . . . and the smoke taken into the mouth can be inhaled very deeply, moderately deeply, slightly, or not at all.

BATCO Group R&D Conference on Smoking Behaviour. October 11-12, 1976. Southampton. Table III. Page BW-W2-02251 (questions whether increase in CO can result when a smoker compensates for reduced nicotine delivery to the mouth.)

Thornton RE. BATCO Group R&D *Some "Benefits" of Smoking.* Report No. RD 1461. January 26, 1977.

Courtney JR, Comer AK. BATCO Group R&D *The Study of Human Smoking Behaviour Using Butt Analysis.* Report No. RD 1608. August 7, 1978.

Lee, note 322, *supra.*

Read G, Anderson IGM, Chapman RE. BATCO Group R&D *Nicotine Studies: A Second Report. Estimation of Whole Body Nicotine Dose By Urinary Nicotine and Cotinine Measurement.* March 31, 1981. Pages 9-10.

Proceedings of the BATCO Smoking Behaviour-Marketing Conference, Session III. July 9-12, 1984. Slides at p. BW-W2-02748-02750, 02754-02759.

Id. Koehn E. Potential of nicotine addiction. Page 64, BW-W2-02651.

Id. Pangritz D. Discussion (Minutes). Page 65, BW-W2-02647-02651.

R.J. Reynolds, note 300, *supra,* at pp. 479, 482-3, 490-2.

Tobacco Advisory Council. *Reduction in Sales Weighted Average Cigarette Brand Tar Yield: Problems Associated with the Suggestion to Achieve Further Stages According to a Fixed Timetable* (prepared by TAC for members of the Independent Scientific Committee on Smoking and Health) at p. 3:

There are circumstances in which smokers, when switching to a brand with a reduced tar yield, will tend to 'compensate' whether consciously or subconsciously, if they find some aspect of a new cigarette less acceptable than that of their normal brand, in such a way as to restore to some extent the loss of satisfaction associated with the reduced tar yield itself, or associated with some inevitable consequence of the reduced tar yield, for example reduced nicotine yield. . . .

nicotine from each cigarette. For example, Senior Philip Morris scientist William L. Dunn wrote to an outside researcher in 1975 that smokers compensate for reduced nicotine in cigarettes through a variety of techniques designed to increase the amount of nicotine that enters the bloodstream:

> *The ultimate index [of nicotine consumption] is how much passes over into the bloodstream . . . We're now looking at the fate of the smoke entering the mouth; how much goes down, how much comes back out, and related behavioral events that we anticipate finding to be dose-regulating mechanisms of remarkable precision and sensitivity.*
>
> *Thus to accommodate to the 15 percent reduction in available Marlboro nicotine, the smoker who was getting 50 percent of the available nicotine over into his blood from the Marlboro delivering 1.1 mg of nicotine into a smoking machine now must get 59 percent of what the current Marlboro offers him. He can take bigger puffs, or inhale more from the supply drawn into the mouth . . . or for more efficient extraction of the goodies, he can draw it in deeper or hold it longer.*[323a] [Emphasis added.]

[323a] Letter to Stanley Schachter, Columbia University from William L. Dunn. September 8, 1975. *In* Cong Rec. H7662 (daily ed. July 25, 1995).

See also:

Memorandum to T.S. Osdene from W.L. Dunn. Behavioral Research Accomplishments-1977. December 19, 1977. *In* Cong Rec. H7666, *supra*:

> *[N]icotine compensation is a real phenomenon . . .*

In this report, the researchers describe a study confirming their hypothesis that "some people smoke for nicotine, and that these people try to obtain a relatively constant amount of nicotine from their cigarettes." The internal study showed that smokers they called "nicotine regulators" obtained more nicotine from their cigarettes following a period of deprivation than when allowed to smoke freely.

Dunn WL. 1600/Smoker Psychology/January 1-31, 1976 [Monthly Report]. February 10, 1976. *In* Cong Rec. H7663, *supra*. This report describes a new study being undertaken by Philip Morris "to identify nicotine regulators and non-regulators." The study design involved measuring "the daily nicotine intakes" of a group of smokers when allowed to smoke their own cigarettes, then measuring their nicotine intakes when given cigarettes with higher or lower delivery than their own brand:

> *We want to find out if we can "force" our potential regulators to modify their puff volumes, inhalation volumes, and/or smoke retention times in order to obtain their usual nicotine dose.* [Emphasis added.]

Memorandum from W.L. Dunn to T.S. Osdene. Quarterly Report - January 1-March 31, 1975. March 25, 1975. *In* Cong Rec. H7662, *supra*. Reports on a Philip Morris study showing compensation behavior in smokers:

> *Preliminary data suggest that more cigarettes are smoked and more puffs taken when the observations follow a two-hour deprivation period than following two hours when smoking is*

In 1984, the minutes of the BATCO Smoking Conference included the following summary of the researchers' discussion of compensation:

> *Compensation*
>
> *There are two general forms of compensation:*
>
> *a) Number of cigarettes smoked eg. [sic] low tar smokers increasing consumption.*
> *b) Puffing/inhalation regime eg. [sic] increasing or decreasing/puff volume, duration, puff frequency, amount inhaled.*[324]

The researchers further stated that:

> *it is accepted that nicotine is both the driving force and the signal (as impact) for compensation in human smoking behaviour.*[325]

In fact, the tobacco industry is not merely aware of compensation behavior but has conducted extensive research on compensation. Company researchers administer cigarettes that deliver a range of nicotine doses to smokers and then measure the amount of nicotine

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permitted.

Dunn WL. 1600/Smoker Psychology/October 1-31, 1977 [Monthly Report]. November 11, 1977. *In* Cong Rec. H7665, *supra*. Philip Morris researchers describe a study on whether smokers who smoke many cigarettes out of "need" will demonstrate compensation behavior if given low nicotine cigarettes.

Memorandum to T.S. Osdene from W.L. Dunn. Plans and Objectives - 1980. January 7, 1980. *In* Cong Rec. H7665, *supra*. This document describes Philip Morris' development of specialized monitoring devices designed to determine whether smokers, when given cigarettes with different nicotine deliveries "regulate or 'titrate' the amount of nicotine taken up via inspiration of smoke."

[324] Brooks GO. Minutes from BATCO Group R&D Smoking Behaviour-Marketing Conference, Session III. July 9-12, 1984. Page 55.

[325] *Id.* at p. 56.

Later at the same conference, there was a discussion of a study showing that when given a cigarette with a significantly different yield than his own, a smoker will alter his puffing behavior but will not alter his inhalation pattern. To explain this phenomenon, "[d]elegates were reminded that a smoker extracts virtually all of the nicotine from the smoke even with a shallow inhalation. Therefore what has he to gain by deliberately inhaling more deeply?" *Id.* at p. 69.

actually absorbed by the smoker, per puff or per cigarette.[326] These studies show that smokers tend to obtain close to the same amount of nicotine from each cigarette, despite differences in yield as measured by the smoking machine. In a 1974 BATCO conference, researchers described the results of one such study:

> *The Kippa study in Germany suggests that whatever the characteristics of cigarettes as determined by smoking machines, the smoker adjusts his pattern to deliver his own nicotine requirements (about 0.8 mg. per cigarette).* [Emphasis added.][327]

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[326] *See:*

BATCO Group R&D Conference on Smoking Behaviour. Southampton, England. October 11-12, 1976. Page BW-W2-02253-85.

Adams PI. Research Dept., Imperial Tobacco Ltd. Changes in personal smoking habits brought about by changes in cigarette smoke yield. In: *Proceedings of the Sixth International Tobacco Scientific Congress.* November 1976. Pages 102-108.

BATCO, note 310, *supra,* at p. 2.

> *Although conflicting results were presented, the prevailing view is that smokers do tend to compensate in some way when going from a high tar (nicotine) to a low tar (nicotine) cigarette, or vice versa. Studies have been carried out with high and low nicotine cigarettes, "anti-smoking" cigarette holders, and cigarettes with shortened tobacco sections.*

Pritchard WS, Robinson JH. The sensory role of nicotine in cigarette "taste", smoking satisfaction, and desire to smoke. As abstracted in: *International Symposium on Nicotine: The Effects of Nicotine on Biological Systems II.* Satellite Symposium of the 12th International Congress of Pharmacology. Montreal, Canada. July 21-24, 1994. Page 113.

See also:

Ashton H, Stepney R, Thompson JW. Self-titration by cigarette smokers. *British Medical Journal.* 1979;2:357-360.

[327] Notes on the BATCO Group R&D Conference at Duck Key, FL. January 12-18, 1974. (Attended by Hughes, Sanford, Esterle of B&W). Page 2.

See also Notes from the German presentation. BATCO Group R&D Conference 1979. Part I, February 5-9, 1979. Page BW-W2-03536:

> *One of the interesting results from the KIPA studies is that cigarettes which vary from 1.1 - 0.4 mg nicotine by machine smoking are smoked by humans in the narrow range of 0.8 - 0.7 mg nicotine.*

At a 1984 conference, a BATCO researcher also reviewed several other studies indicating that when smokers are given cigarettes with higher or lower nicotine levels than their regular brands, they tend to adjust both the number of cigarettes they smoke and the way they smoke them to attain a steady dose of nicotine.[328] In support of this conclusion, the BATCO researcher presented a chart showing that between 1965 and 1975, as the machine-measured nicotine yield of cigarettes went down, the annual consumption of cigarettes per smoker went up.[329]

The researcher concluded that "increased consumption is related to reduced nicotine"[330] but that the relationship is not one-to-one. Instead, he found that a 10% reduction in nicotine resulted in a 1% rise in the number of cigarettes smoked, and a 50% reduction in nicotine resulted in a 10% rise in the number of cigarettes smoked.[331] As a result of this finding, he concluded that "most compensation must occur at the individual cigarette level;"[332] i.e., by altering the way the smokers smoked individual cigarettes. In fact, the data he presented showed that when smokers were given cigarettes with a range of nicotine yields, their nicotine intake from each cigarette hovered around the amount they took in from their regular brand rather than varying to the degree that would have been predicted from the

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[328] Proceedings of the BATCO Smoking Behaviour-Marketing Conference, Session III. July 9-12, 1984. Ferris. Pages BW-W2-02748 - 02750, BW-W2-02754 - 02759.

[329] *Id.* at p. BW-W2-02754.

[330] *Id.* at p. BW-W2-02755.

[331] *Id.*

[332] *Id.*

machine yields.[333]

Other tobacco company studies show similar results.[334] A report on research conducted by Philip Morris Europe in the early 1970's concluded that smokers tended to obtain the same amount of nicotine from a cigarette, regardless of the nicotine content of the cigarette or its machine-tested yield:

> *The most frequent nicotine yield was 0.4 to 0.5 mg of nicotine per cigarette. This yield is not dependent upon the nicotine content of the tobacco and is not related to the nicotine yield under Coresta (machine) smoking conditions. The difference between nicotine yields obtained under standard laboratory procedures and yields obtained under "real" smoking conditions is explained by the existence of a compensation mechanism in the smoker. This compensation mechanism seems to be in operation for a proportion of the consumer population to adjust the nicotine yield to their needs or liking.*[334a]

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[333] *Id.* at p. BW-W2-02757. Ashton, Stepney, and Thompson (1979b). *Expected and observed nicotine intake in a brand-switching experiment.* (Chart.)

[334] *See:*

BATCO Group R&D Proceedings of the R & D Conference. Montreal, Canada. October 25, 1967. Page 4.

> *The development of low TPM [total particulate matter], low nicotine cigarette should be expanded. This raises the question of the level of nicotine required and the consumer study by Bristol can be helpful in determining this . . . there was evidence that in Germany per capita cigarette consumption increased for the lower nicotine brands.*

Proceedings of the BATCO Group R&D Smoking Behaviour-Marketing Conference, Session I. July 9-12, 1984. Presentation slide BW-W2-03231. Under the heading *Brand Switching Down Delivery*, the chart provides a list of three "means to achieve a higher dose[:] . . . increase in puffing parameters, increase in numbers of cigs. smoked, more puffs taken."

Read GA. Internal v. external studies. Proceedings of the BATCO Smoking Behaviour-Marketing Conference, Session II. July 9-12, 1984. Page 19.

> *The German butt analysis studies have indicated how smokers respond to reductions in machine smoked nicotine deliveries under natural smoking conditions. This observation of product oversmoking supports the laboratory findings of an increase in smoking behaviour parameters in subjects switched to lower delivery products.*

R.J. Reynolds, note 300, *supra,* at pp. 479, 482-3, 490-2.

[334a] Gustafson and Haisch. PME Research: 1972-1974. *In* Cong Rec. H7662 (daily ed. July 25, 1995).

[Emphasis added.]

Thus, the tobacco companies' own studies demonstrate that smokers use the cigarette as a nicotine delivery system and vary their smoking behavior to obtain a specific dose of nicotine.

4. Industry Research and Knowledge of Tobacco Users' Inability to Quit

Tobacco companies are aware of the large number of smokers who have tried to quit using tobacco, and of the very small number who actually succeed. The evidence known to tobacco companies about smokers' unsuccessful attempts to quit shows that tobacco companies know that a large percentage of their market consists of people who demonstrate one of the characteristic features of addiction. See p. 81 et seq.

The great difficulty smokers experience when they try to quit was conceded by Joseph F. Cullman, III, the former chief executive officer of Philip Morris. Mr. Cullman was called as a witness in the Cipollone lawsuit and gave the following answers in response to questions from one of the plaintiff's attorneys:

Q. But it is difficult [to quit]?

A. That's what it says here and I'm not disagreeing with it.

Q. They said it was very difficult. Do you agree with that?

A. I would say it's difficult.

Q. And it's difficult for the vast majority of smokers, you would agree with that, too, would you not?

A. That's a question of semantics. What's the vast majority? A lot of smokers have a hard time quiting [sic].

Q. Let's see, most smokers have a tough time giving up cigarettes?

A. Well, if they didn't, there would be many fewer smokers than there are today.[335] [Emphasis added.]

Furthermore, internal Brown and Williamson documents reveal that the tobacco

[335] Examination of Joseph Cullman, III, former chief executive officer, Philip Morris, Inc. *Cipollone v. Liggett Group, Inc., et al.*, Civil Action No. 83-2864 (SA)(D.N.J.). February 29, 1988. Afternoon Session. Transcript of proceedings, at pp. 3311-3314.

industry is extremely interested in rates of attempted and successful quitting, and keeps close track of these rates. At the 1984 BATCO Smoking Behaviour-Marketing Conference, attended by representatives from various BATCO companies, including Brown and Williamson, each of the participating companies was asked to fill out a questionnaire that asked how many smokers in their respective countries attempted to quit in each of the previous 5 years and how many actually quit (for as long as 6 months). Brown and Williamson's response to the questionnaire, which covered quitting rates in the United States, reported that, for the years 1981 through 1983, 32 million to 34 million Americans attempted to quit each year, while only 9 million to 10 million of those were able to quit for as long as 6 months.[336] Thus, Brown and Williamson's own data reveal that while almost half the total number of U.S. smokers attempted to quit each year, only about a third of those who tried to stop smoking were able to quit for as long as 6 months. These tobacco industry data suggest that at least one-third of U.S. consumers of cigarettes are purchasing cigarettes because they are unable to stop smoking.

In fact, data reported at the same conference showed that the percentage of smokers who continue to smoke even though they do not want to is much higher than suggested by 6-month data. Data from the Canadian tobacco company representatives indicated that rates of permanent quitting were well below quitting rates reported at 6 months. A Canadian participant reported to the assembled BATCO researchers that only 10% to 12% of those Canadian smokers attempting to quit succeeded for up to 1 year; less than 4% were able to

[336] Proceedings of the BATCO Smoking Behaviour-Marketing Conference, Session I. July 9-12, 1984. Page BW-W2-03212. No figures were provided by B&W on attempts to quit for the years 1979 and 1980.

quit permanently.[337]

The presenter responsible for summing up the results of the conference questionnaire agreed that, while a large percentage of smokers do not want to smoke, most of those smokers feel compelled to continue to smoke:

> *Although intentions and attempts to quit are relatively high (30-40% of smokers [in a given year]), the actual success rate of quitting is relatively low and stable.*[338]

It was thus well known to the participating companies that a very large percentage of their customers were smoking not out of choice but because they could not quit.

Other companies also understand that many of their consumers would like to quit but are unable to do so.[339] A Philip Morris researcher who studied a "cold turkey" campaign in

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[337] Proceedings of the BATCO Group R&D Smoking Behaviour-Marketing Conference. July 9-12, 1984. Session IV. Page BW-W2-03381. *See also* Session III at p. 83 (BW-W2-03379-03382). The researcher also presented data showing that while 22% of smokers claimed that they intended to "cut down," in fact "both the claimed and calculated rate of daily usage (21.6 and 25.6 [cigarettes] respectively) have increased since the introduction of lights." (BW-W2-02790, 03379, 033820). Other data reported at the same conference provided additional confirmation of the large percentage of smokers who would prefer not to smoke. A study on "Smoker Consonance-Dissonance Breakdown" was presented which showed that approximately 75% of smokers surveyed had attempted to quit, and approximately 60% were currently serious about quitting. Session III at p. BW-W2-03386.

See also, Larsen PS, Silvette H. *Tobacco Experimental and Clinical Studies: A Comprehensive Account of the World Literature, Supplement I.* (1968), Chapter 15; *Supplement II* (1971), Chapter 17; *Supplement III* (1975), Chapter 21, which contain discussions of surveys concerning smokers' desire to quit and difficulty in successfully quitting. This review was funded by the Council for Tobacco Research.

[338] Proceedings of the BATCO Smoking Behaviour-Marketing Conference, Session IV. July 9-12, 1984. Page 12.

[339] *See:*
R.J. Reynolds Tobacco Company, response to Citizen Petitions 94-0069/CP1 and 94P-0077/CP1. November 2, 1994. Pages 66-69.

RJR-MI Brand Group and Ogilvy & Mather (Canada) Ltd. *Vantage Brand Positioning Statement.* 1979. Page 80041:

B. User Image

Primarily female, white collar, extremely concerned about their health, and would like to

the small Iowa town of Greenfield in 1969 reported that those who succeed in quitting smoking over the long term are a much smaller group than those who would like to quit and who attempt to quit.[340] The researcher cited the findings of Hunt and Matarazzo[341] in proposing that most attempts to quit smoking are not long-lasting: "[I]n summarizing many reports of long-term quitting using various techniques, [the authors] show that the percentage of nonrecidivists [successful quitters] decreases as a function of time . . . in a negatively accelerated fashion."[342] The Philip Morris researcher found that in Greenfield only 28% of those smokers who agreed to quit as part of the cold turkey campaign were still not smoking after 7 months. The researcher then observed that the small number of Greenfield residents who managed to stay off cigarettes for more than 7 months was, based on other published reports of success rates for quitting smoking, about average.[343]

The researcher also described findings that revealed in part why it is so hard for smokers to quit. He reported that smokers who quit for more than 7 months continued to

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quit smoking.

Kwechansky Marketing Research for Imperial Tobacco Ltd. *Project 16*. October 18, 1977. Page vi.

Kwechansky Marketing Research for Imperial Tobacco Ltd. *Project Plus/Minus*. May 7, 1982. Page i.

[340] Ryan FJ. Philip Morris Research Center. Cold turkey in Greenfield, Iowa: a follow-up study. In: Dunn WL, ed. *Smoking Behavior: Motives and Incentives*. Washington, DC: VH Winston & Sons; 1973:231-241.

[341] *Id.* at p. 233.

[342] *Id.* at p. 233.

[343] Ryan FJ. Bird-I. A study of the quit-smoking campaign in Greenfield, Iowa, in conjunction with the movie, *Cold Turkey*. Appendix 1, p. 1000348712. The author also appended to the unpublished version of this report excerpts from internal company memos, pointing out that although the cold turkey campaign in Greenfield was as intense an anti-smoking effort as could be imagined, "carton sales at the Super Value store have shown a strong increase since the dog days of August."

suffer a variety of adverse effects related to quitting, including weight gain, restlessness, depression, ill-temper, constipation, nervous mannerisms, and loss of energy.[344] These are some of the classic symptoms of nicotine withdrawal, described earlier.[345]

Market research documents also show that tobacco companies have conducted research in quitting behavior and have documented the reasons why people quit and why they fail to quit, despite a desire to do so.[346] A market research firm reporting on a survey of smokers' views about the health implications of smoking observed that:

> *a minority expresses a resentment about the addictive aspects of smoking. Being "out of control," unable to quit causes them to feel somehow unworthy . . . . Nicotine is usually singled out as the culprit here. However, even these smokers would be reluctant to give up the satisfaction elements in smoking. So they are in a quandry [sic]."* [347]

Another market research firm reported its findings about the inability of young smokers to quit when they want to:

> *However intriguing smoking was at 11, 12 or 13, by the age of 16 or 17 many regretted their use of cigarettes for health reasons and because they feel*

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[344] *See* Ryan, note 340, *supra,* at p. 234.

[345] *See* FINDINGS § I.B., *supra.*

[346] *See e.g.* The Creative Research Group. *Project Viking, Vol. III: Product Issues.* Prepared for Imperial Tobacco Ltd., Feb/Mar 1986.

Kwechansky Marketing Research for Imperial Tobacco Ltd. *Project Plus/Minus.* May 7, 1982. Pages 41-51.

[347] The Creative Research Group. *Project Day-Exploratory Phase in Edmonton.* Prepared for Imperial Tobacco Ltd. August 1988. Page 11.

See also Market System, Inc. *Project Eli Focus Groups Final Report.* Prepared for Imperial Tobacco Ltd. July, 1982. Page 5. Smokers refer to smoking as "satisfying a craving."

unable to stop smoking when they want to.[348]

The fact that many smokers smoke even though they do not enjoy smoking is conceded in a candid marketing research document prepared for Imperial Tobacco Ltd., which reported that it is particularly difficult to sell cigarettes by "trading on the positives" because the industry is "vexed by the unique problem that users of the category do not necessarily like the product."[349] Another document reports that many smokers of ultra-low tar and nicotine cigarettes want to quit and "refer to their behavior in terms of 'satisfying a craving' while smokers of stronger cigarettes talk about taste and satisfaction."[350]

In summary, the tobacco companies' data show that users find it extremely difficult to quit smoking and that many tobacco users would quit if they could. Their data also show that, of those smokers who try to quit, only a small percentage succeed permanently. Consequently, tobacco manufacturers are aware that the large percentage of their customers who try to quit but fail continue to buy and use tobacco products, in large part to satisfy their dependence on nicotine-containing tobacco. Use of tobacco to satisfy nicotine dependence is

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[348] *See* Kwechansky Marketing Research. *Project 16*, note 339, *supra,* at p. vi.

See also Kwechansky Marketing Research. *Project Plus/Minus*. May 7, 1982. Study Highlights. In a follow-up study, the same market research firm reported the following results:

> *The desire to quit seems to come earlier now than before, even prior to the end of high school....However, the desire to quit, and actually carrying it out, are two quite different things, as the would be quitter soons [sic] learns...*

According to a report in *Newsday*, a 1957 "motivation survey" prepared for Liggett on smoker attitudes about smoking amid growing health concerns contained the following statement:

> *What smokers are really saying is: 'I wish I had never started to smoke . . . but now that it's got me, I know that I can't stop.'*

Riley J. Smoke-Trial Documents Make Titillating Reading. *Newsday.* July 19, 1988.

[349] *See* The Creative Research Group Ltd., note 346, *supra,* at p. 64451.

[350] *See* Market System Inc., note 347, *supra,* at p. 5.

a use that affects the structure or function of the body.

D. INDUSTRY PRODUCT DEVELOPMENT RESEARCH TO ENSURE AN ADEQUATE DOSE OF NICOTINE

1. Industry Emphasis on Nicotine in Product Development Research

Tobacco industry documents show that adequate nicotine delivery is a dominant consideration in product development research. As discussed above, many tobacco industry documents demonstrate the industry's understanding that the amount of nicotine delivered from tobacco must not fall below a certain threshold.[351] These and other documents also reflect the industry's recognition that below that threshold, tobacco fails to deliver a pharmacologically active dose of nicotine, and that consumers will reject the resulting product. The documents described in this and the next section reveal the industry's extensive product development research to maintain or increase nicotine delivery from tobacco products.

Industry patents disclose that the industry has long recognized the importance of developing methods to maintain or increase the amount of nicotine in tobacco, and that the purpose of these methods is to ensure that consumers experience nicotine's pharmacological effects. For example, a patent held by Philip Morris states:

> *Maintaining the nicotine content at a sufficiently high level to provide the desired physiological activity, taste, and odor . . . can thus be seen to be a significant problem in the tobacco art. The addition of nicotine to tobacco in such a way that it remains inert and stable in the product and yet is released in a controlled amount into the smoke aerosol when the tobacco is pyrolyzed, is a*

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[351] *See* documents cited in FINDINGS § II.C.1. and 2.

See also F.H. [Initials of BATCO R&D employee] Memorandum. *Developments in the Product in the Next Ten years.* 1973-1974. Page 3. ("The maintenance of adequate levels of nicotine in cigarettes could become a difficult problem as more synthetics are used.")

result which is greatly desirable. [Emphasis added.][352]

In fact, over the past several decades, enhancing and optimizing nicotine delivery has been a major focus of tobacco industry product design research. The American Tobacco Company (ATC) devoted substantial research to finding methods of increasing the amount of nicotine delivered by its cigarettes. For example, in 1963, ATC conducted research on increasing the nicotine yield in Lucky Strike cigarettes by increasing the proportion of Burley tobacco, a high-nicotine tobacco, in the tobacco blend used to make the cigarettes.[353] The company found that it could increase the nicotine yield of the cigarettes up to 10% in this manner and that smokers perceived the resulting cigarettes as having more "strength."[354] In 1969, ATC test-marketed Lucky Strike cigarettes that had been enriched with added nicotine.[355] ATC developed other methods for increasing the amount of nicotine delivered by its cigarettes over the subsequent decades, including:

- the use of carbon tips in the filter "impregnated with nicotine or nicotine salts" to

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[352] U.S. Patent No. 3,280,823. Bavley A, Air D, Robb E II. *Additive-Releasing Filter for Releasing Additives into Tobacco Smoke.* Philip Morris, Inc. October 25, 1966. Page C1:43-48.

[353] "Tobacco Blends for Filter Cigarettes: Effect of Increasing the Concentration of Burley Tobacco in a Blend" at Page 1. June 21, 1963. The various ATC documents discussed in this section were provided by the company to the Subcommittee on Health and the Environment of the House Energy and Commerce Committee, and attached as exhibits to the Dec. 20, 1994, Subcommittee Staff Report, entitled, "Evidence of Nicotine Manipulation by the American Tobacco Company."

[354] *Id.* at pp. 4, 5. The company again experimented with increasing the nicotine content of Lucky Strikes through changes in the tobacco blend in 1968. Memo to Mr. H.V.H. Stoever, Jr., Manager, Durham Branch, from O.N. Coty, Manager-Quality Control, Research and Development (June 4, 1968). Pages 1-2; Tables X003384-3387. *See also* memo to R.F. MacDonald from O.N. Coty, July 5, 1968.

[355] Letter from Chadbourne & Park, representing ATC, to the Honorable Henry A. Waxman, Chairman, Subcommittee on Health and the Environment of the House Committee on Energy and Commerce. Oct. 14, 1994. Page 3 of attachment to ATC Response.

increase the nicotine content of cigarette smoke;[356]

- direct addition of commercial nicotine to reconstituted tobacco;[357]
- addition of nicotine to the "finishing flavor" used in Pall Mall 85's;[358]
- growing tobacco plants in different locations to determine, among other things, whether varieties with different ratios of nicotine to tar could be produced;[359]
- addition of nicotine to the "dip casing" (one of several solutions used in the manufacture of cigarettes) to compensate for loss of nicotine from other manipulations

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[356] Memo to E.S. Harlow from ATC Analytical Chemistry Section, Group I, Aug. 8, 1963, Progress Report, March 1962-July 1963," with attached smoke analysis 2-12-68, 2-1-68, 1-29-68, 1-15-68, 1-4-68, 12-28-67, 12-22-67 (impregnating a carbon tip with nicotine permitted transfer of about 22% of the added nicotine to the smoke).

[357] ATC experimented with adding nicotine to reconstituted tobacco on several occasions. *See*:

"The Effect of the Addition of 1% Nicotine on the Quality of RC Tobacco" (Oct. 8, 1963) (nicotine citrate was added to reconstituted tobacco to triple its nicotine content, from about 1/2% to about 1 1/2%). Pages 1,2,6.

"Evaluation of Nicotine-Fortified RC-A Tobacco" (May 2, 1968) (nicotine malate was added to reconstituted tobacco to increase its nicotine content from .94% to 1.27%; the company concluded that "to markedly improve RC [reconstituted tobacco] . . . in addition to increasing its nicotine content it should also include the other constituents present in natural leaf tobacco, particularly those tobaccos of high nicotine content."). Pages 1-2.

Memo to J.B. McCarthy, Executive Vice President, from R.M. Irby, Jr., Manager-New Products Div., Research and Development, "Nicotine Content of Reconstituted Tobacco." June 5, 1974. (Nicotine added to tobacco extract which is applied to reconstituted tobacco, doubling the nicotine content of the reconstituted tobacco from 0.9% to about 1.8%.) Page 1.

[358] Memo to E.S. Harlow from O.N. Coty *Special PALL MALL 85's with added nicotine.* July 12, 1968. (Nicotine content of final blend increased by 0.47%; smoke panel preferred regular blend.)

[359] Memo to Dr. E.C. Cogbill, Manager-Analytical Research, Research and Development from J.M. Moseley Manager-Basic Materials Research, Research and Development. *Genetic Variation in "Tar" Delivery.* January 8, 1969.

of the tobacco blend;[360]

- addition of nicotine to both Pall Mall and Lucky Strike cigarettes, increasing their nicotine content 35% per cigarette (41% per puff for Pall Mall, slightly less per puff for Lucky Strike);[361] and
- addition of nicotine to tobacco stems (which are used in the manufacture of cigarettes) to increase their nicotine content from 0.5% to 1.87%.[362]

ATC also considered replacing the tobacco used in its reconstituted tobacco with "high nicotine tobacco such as Malawi sun-cured scrap (5% nicotine)" to increase the nicotine content from 0.9% to about 1.6%,[363] increasing "nicotine transfer to the smoke" by dilution or use of filter additives,[364] and increasing, in various ways, the proportion of nicotine relative to tar by adding nicotine to the tobacco, the filter, and the cigarette paper.[365]

Philip Morris documents show that it, too, conducted research on altering and optimizing nicotine delivery from its cigarettes. According to a 1972 memo from William

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[360] Memo to Mr. J.B. McCarthy, Vice President, Manufacture and Leaf from J.T. Ashworth, Manager - Process Development, Research and Development. "Experimental *LUCKY STRIKE Cigarettes (RC-E)*." May 29, 1969. (The author recommends that the experimental cigarettes with added nicotine replace the regular Lucky Strike brand; these may be the cigarettes that were test marketed in 1969). This memo refers to nicotine as "Compound W". An earlier ATC memo instructs employees to refer to nicotine as "Compound W" in all future experimental work, reports, and memorandums. ATC memo to W.W. Sadler, J.G. Brooks, and R.D. Chumney, from John T. Ashworth, "Compound W" (May 14, 1969).

[361] Memo to Mr. V.B. Lougee, III, from R.M. Irby, Jr. *Compound W.* April 29, 1974. Pages 1-2.

[362] *Id.* at p. 2.

[363] Irby memo, note 357, *supra,* at p. 2.

[364] *Id.* at p. 3.

[365] Memo to Dr. P.H. Leake from P.M. Pedersen, transmitting a copy of *A Study of the Nicotine to Tar Ratio.* April 18, 1977. Pages 3-4.

Dunn, a senior official at Philip Morris, research was underway to identify optimal nicotine levels for menthol cigarettes:

> *This study has a three stage design. The first stage is designed to identify those nicotine delivery levels which we might reasonably wish to consider for menthol cigarettes. Having identified these nicotine delivery levels, in stage 2 we will determine combinations of nicotine and menthol which make for optimal acceptability. And then in stage 3, cigarettes with these combinations will be tested against current brands of known quality and sales potential.*[365a]

Philip Morris was thus engaged in research in which nicotine delivery was systematically manipulated, independent of other tobacco variables.

Industry patents from various tobacco companies show that substantial research throughout the industry has been directed at developing methods for selectively increasing nicotine levels and the amount of nicotine delivered by tobacco products.[366] BATCO documents show significant research efforts directed at increasing nicotine delivery. A 1978 BATCO R&D Conference included a discussion of the economic importance of increasing the proportion of nicotine that is actually delivered from the tobacco to the smoker during the consumption of the product:

[365a] P.A. Eichorn and W.L. Dunn. Quarterly Report-Projects 1600 and 2302. October 5, 1972. *In* Cong Rec. H7649 (daily ed. July 25, 1995).

[366] *See, e.g.*:

U.S. Patent No. 5,031,646 at C5:65-68 ("nicotine can be incorporated into the expansion solvents used to provide a volume expanded processed tobacco material having a high nicotine content").

U.S. Patent No. 4,676,259 at C2:30-33, 53-56 ("The present invention provides a nicotine-enhanced smoking device with a high nicotine release efficiency").

U.S. Patent No. 4,898,188 at C1:37-47 (utilizing supercritical extraction to transfer nicotine from high-nicotine tobacco to lower-nicotine tobaccos, thereby increasing the nicotine content of the latter).

U.S. Patent No. 5,065,775 (describing technology for modifying the nicotine content of tobacco filler, enabling a manufacturer to double the nicotine content of tobacco).

With conventional cigarettes, the transfer of nicotine to the smoker from the tobacco has very low efficiency. Potentially, therefore, opportunities exist for very big savings in tobacco if this low efficiency can be greatly increased.[367]

In other words, BATCO wanted to increase the amount of nicotine delivered to the consumer without changing the amount of nicotine already present in the tobacco. (This is what one or more tobacco companies have in fact achieved by the use of the "ammonia technology" described in § II.E., infra.) A 1968 BATCO study approached the objective of enhancing nicotine delivery from a different angle. This study was intended to help develop methods of increasing the smoker's absorption of nicotine, while decreasing other undesirable physiological effects of inhaling tobacco smoke. The study examined the factors that influence the amount of nicotine that is absorbed from tobacco through the oral mucosa (mouth), with an eye toward designing products that would increase nicotine absorption in the mouth, thus avoiding or reducing the need to inhale smoke into the lungs. The study authors maintained that:

If it can be shown that appreciable amounts of nicotine can be absorbed via the mouth, and which factors contribute to enhanced absorption, it may be possible to design cigarettes so that it would only be necessary to inhale the smoke to a very limited extent.[368]

This focus on absorption makes clear that the industry's primary interest is in delivering nicotine to the blood for its systemic effects, rather than in the immediate sensory effects in the mouth (e.g., flavor). Methods of optimizing nicotine delivery were also discussed at two

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[367] BATCO Group Research & Development Conference, Sydney. March 1978. Page 4. Notes on Group Research R&D.

[368] Evelyn SR. BATCO Group Research & Development. *Absorption of Nicotine via the Mouth: Studies Using Model Systems*. Report No. RD 560-R. May 9, 1968. Page 4.

separate BATCO R&D conferences in 1984.[369]

The industry has also developed product design options to manipulate the amount of nicotine delivered to ensure smoker satisfaction, even at the level of the individual puff. For example, an industry patent states:

> *It is a further object of this invention to provide a cigarette which delivers a larger amount of nicotine in the first few puffs of the cigarette than in the last few puffs.*[370]

The focus on nicotine delivery in product development and the fact that nicotine manipulation is intended to ensure that consumers experience nicotine's pharmacological effects is also shown by the tobacco industry's research to improve tobacco "satisfaction." "Satisfaction" is one of the industry's principal product development research objectives. As already described in FINDINGS § II.C.1., supra, the term "satisfaction" is generally used by the tobacco industry to refer to the ability of a tobacco product to satisfy the consumer's desire for the pharmacological

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[369] *See* BATCO Group R&D Research Conference. September 1984. Proposed Revisions for 1985-1987. Pages 1-2:

> *The experimental cigarettes used in 1(b)[denicotinized, then supplemented with varying levels of nicotine] will also be used to improve the efficient use of smoke nicotine through pH modification. These studies will identify the relationship between nicotine dose and nicotine-related subjective improvement. This will further help to identify the relationship between product acceptability and smoker satisfaction.* [Emphasis added.]

Proceedings of the BATCO Group R&D Smoking Behaviour-Marketing Conference, Session III. July 9-12, 1984. Ferris at p. 81:

> *How we use this perspective in terms of marketing action requires careful consideration since most of this evidence is ostensibly of industry strategic defence value. However product development to optimise efficiency of nicotine delivery, and a better understanding of the "visual-tactile" smoker (albeit limited segment) are obvious starting points.* [Emphasis added.]

[370] U.S. Patent No. 4,595,024. Greene TB, Townsend DE, Perfetti TA. *Segmented Cigarette*. R.J. Reynolds Tobacco Company. June 17, 1986. C2:23-26.

See also U.S. Patent No. 3,280,823 Bavley A, Air B, Robb II EW. *Additive-Releasing Filter for Releasing Additives into Tobacco Smoke*. Philip Morris Inc. October 25, 1966. C2:37-40 ("This invention permits the release into tobacco smoke, in controlled amounts . . . and when desired of nicotine into tobacco smoke").

effects of nicotine, and is understood by the industry as an essential component of consumer acceptance of tobacco products. The conferees at a 1983 BATCO Research Conference in Rio de Janeiro sought to expand research efforts on nicotine as the principal source of smoker satisfaction and to "develop products that give improved smoker satisfaction."[371] The conferees agreed that to achieve this goal, BATCO must know as much as possible about nicotine, including:

- *factors that affect the transfer of nicotine from leaf to smoke aerosol*
- *factors that influence the rate of transfer of nicotine from particulate matter to the vapour phase*
- *the contribution of nicotine to smoke sensory characteristics (including harshness and irritation)*
- *the site and mechanisms of absorption of nicotine within the human system*
- *the way nicotine stimulates both the central nervous system and the peripheral organs (eg heart and lung)*
- *the metabolism of nicotine within the body, including rates and equilibrium levels.* [Emphasis added.][372]

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[371] BATCO Group R&D Research Conference. Rio de Janeiro, Brazil. August 22-26, 1983. Page BW-W2-01837.

[372] *Id.* at p. 13. Philip Morris documents similarly show that that company's research on manipulating nicotine delivery was aimed at ensuring that smokers experience nicotine's pharmacological effects. *See e.g.:*

Philip Morris employee (almost certainly W.L. Dunn). *Smoker Psychology Program Review.* October 19. 1977. This paper sets forth questions being asked by researchers at Philip Morris, at pages 5-6:

a) What is the lower delivery level limit beyond which the smoking act is not reinforced?
b) Within what limits can we vary nicotine concentration relative to other smoke constituents?
1) What is the optimum nicotine/tar ratio?
c) Given a fixed quantity of nicotine in the tobacco, what factors in cigarette design determine its availability for delivery to the smoker?. . . .
e) Does the smoker seek spike effects, bloodstream constancy?. . . .
g) How important is the form of the delivered nicotine? (salt vs. free base? pH? particle size?)

Ryan, FJ, Jones, BW, Martin, PG, Dunn, WL. Behavioral Research Annual Report. July 18, 1975. Page

This list of product development research objectives makes clear BATCO's interest in the delivery of nicotine for absorption into the bloodstream and in its systemic effects once absorbed.

The tobacco industry's product development research on manipulating the amount and manner in which nicotine is delivered to the consumer demonstrates the industry's intent to sell tobacco products that provide a pharmacologically active dose of nicotine.

17:

As deliveries drop we reasoned that eventually they could reach a point where all the cigarettes in a pack would be unsatisfying.

The same document reports on Philip Morris studies of: 1) acceptability of various nicotine/tar ratios in a 10 mg tar cigarette, and 2) methods of producing a low delivery cigarettes "with impact and flavor." Pages 23-25.

Dunn, WL. Project 1600/Consumer Psychology/Annual Report. November 18, 1966. Page 9.

Is the transition to preference for a lower delivery cigarette more explicable in terms of (a) Reduction in sought dosage level, or (b) Adaptation of puffing pattern?

Memo to T.S. Osdene from W.L. Dunn. Plans and Objectives - 1982. November 5, 1981. Discusses Philip Morris research on changes in inhalation behavior and puff parameters as a result of changes in nicotine delivery, and on which parameters influence nicotine retention. Pages 7-8.

2. Industry Research on Maintaining Adequate Nicotine Delivery When Lowering Tar

Product design to ensure adequate nicotine absorption by the smoker appears to have been driven, to a large extent, by the growing awareness of smoking-related diseases and the resulting efforts of the tobacco companies to provide cigarettes that delivered lower quantities of known toxic smoke constituents, in particular tar. However, reducing tar levels tends to also reduce the nicotine content.[373] Thus, the industry has known that in designing lower-yield products, nicotine delivery could not be reduced below a certain threshold.[374] In order to reduce tar while maintaining a level of nicotine delivery that would satisfy consumers' desire for the pharmacological effects of nicotine, the industry has focused considerable attention and research on how to maintain or enhance the amount of nicotine delivered by lower-tar products.

A patent held by Imperial Tobacco Ltd. states that the purpose of the technology described in the patent is to permit a cigarette manufacturer to maintain or increase nicotine levels while lowering levels of "undesirable" smoke constituents:

> *[This] invention concerns . . . the problem of maintaining or increasing the nicotine content of the smoke whilst avoiding an undesirable level of particulate*

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[373] *See:*
Spears AW, Jones ST. Chemical and physical criteria for tobacco leaf of modern day cigarettes. *Recent Advances in Tobacco Science.* 1981;7:19-39.

Regulation of Nicotine under the Federal Food, Drug and Cosmetic Act: Hearings Before the Subcommittee on Health and the Environment of the House Committee on Energy and Commerce, 103rd Cong., 2d Sess. (March 25, 1994) (statement of AW Spears, at pp. 1-3).

[374] *See* Project Wheat - Part 2 , note 204, *supra,* at p. 48:
Concern for the possible health risks of smoking influences consumers in the direction of trying low delivery brands. . . . However, there is evidence of a conflict between concern for health and the desire for a satisfying cigarette, from which it follows that low tar brands would be much more widely accepted if their nicotine deliveries could be brought within the range required by groups of consumer[s].

matter in the smoke . . .[375]

A 1976 BATCO "Smoking Behavior" conference report states the industry's dilemma more succinctly:

> *[I]n that the 'benefits' of smoking appear to be related to nicotine, we can infer that the 'benefits' of smoking might disappear if cigarettes with low levels of nicotine became the norm . . . .*[376]

Philip Morris conducted research to find the optimum nicotine delivery level and the optimum nicotine-to-tar ratio for low tar cigarettes. In 1970, a company document stated that Philip Morris planned to conduct a test in which it would reduce tar and add nicotine to Marlboro:

> *We are initiating a study of the effect of systematic variation of the nicotine/tar ratio upon smoking rate and acceptability measures. Using Marlboro as a base cigarette we will reduce the tar delivery incrementally . . . and increase the nicotine delivery by adding a nicotine salt [a commercial form of nicotine].*[376a]

A 1972 Philip Morris document identifies the natural nicotine-to-tar ratio in tobacco as 0.07, which is "characteristic of a broad range of natural leaf."[376b] Within the next three years, Philip Morris had studied and found the "optimal" nicotine-to-tar ratio for consumer ratings of acceptability and "strength." A 1975 Philip Morris document containing the results of a study

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[375] U.S. Patent No. 3,861,400. Perkins PR, Bale CR. *Nicotine Fortification of Smoking Products.* Imperial Tobacco Group Limited. January 21, 1975. C1:1-10.

[376] BATCO Group R&D Conference. Southampton, England. October 11-12, 1976. Page 4.

[376a] P.A. Eichorn and W.L. Dunn. Quarterly Report of Projects 1600 and 2302. December 31, 1970. *In* 141 Cong. Rec. H8008 (daily ed. July 31, 1995)(statement of Rep. Waxman). These studies of optimal nicotine/tar ratios were intended to be used "to provide insight leading to new cigaret designs." Philip Morris, USA. Research and Development Five Year Plan, 1974-1978. May 1973. *In* 141 Cong. Rec. H8008, *supra.*

[376b] Memorandum to P.A. Eichorn from W.L. Dunn et al. Plans for 1972. September 8, 1971. *In* 141 Cong. Rec. H8008 (daily ed. July 31, 1995)(statement of Rep. Waxman).

conducted by the company stated that the optimal nicotine-to-tar ratio was about 0.1, higher than the "natural" ratio:

> *This study provides evidence that the optimum nicotine-to-tar (N/T) ratio for a 10mg tar cigarette is somewhat higher than occurring in smoke from the natural state of tobacco.*[376c]

In other words, the study showed that for a given level of tar (10 mg), it was optimal to supply a higher level of nicotine than would occur naturally in tobacco. According to the authors, the study shows that smokers prefer a higher nicotine delivery in low tar cigarettes than the delivery level that would occur if nicotine were allowed to fall proportionately with tar:

> *[T]he experimental cigarette with the moderate level of nicotine addition was rated higher in acceptability than the proportional reduction cigarette and equal to the Marlboro control.*[376d]

A later quote from the same document, reported in the New York Times, indicates that this study was conducted to provide data on how to alter the natural nicotine-to-tar ratio of a low tar cigarette in such a way as to make the cigarette comparable to Marlboro (Philip Morris' most popular high tar cigarette) in consumer acceptability and "strength":

> *We are using the guidelines suggested by this study to attempt to make a 10mg tar cigarette that will equal a Marlboro in both subjective acceptability and strength.*[376e]

[376c] Low Delivery Cigarettes and Increased Nicotine/Tar Ratios, A Replication. Approved by W.L. Dunn and distributed to H. Wakeham. October, 1975. *In* 141 Cong. Rec. H8009 (daily ed. July 31, 1995)(statement of Rep. Waxman).
See also:
Hilts PJ. "Documents Disclose Philip Morris Studied Nicotine's Effect on Body." *New York Times.* June 8, 1995.

[376d] Low Delivery Cigarettes and Increased Nicotine/Tar Ratios, A Replication. Approved by W.L. Dunn and distributed to H. Wakeham. October, 1975. *In* 141 Cong. Rec. H8009 (daily ed. July 31, 1995)(statement of Rep. Waxman).

[376e] Hilts PJ. "Documents Disclose Philip Morris Studied Nicotine's Effect on Body." *New York Times.* June 8, 1995.

The term "strength," as used in industry documents, is associated with nicotine delivery. A Philip Morris document from 1978 describes further studies being conducted by that company to systematically vary the nicotine-to-tar ratio to find the "optimal" ratio for the company's ultra low (5-7 mg) tar products.[376f]

As early as 1965, a Brown and Williamson official reported to other Brown and Williamson executives that BATCO research was focused on "the smoking and health problem" and that:

> *Their approach seems to be to find ways of obtaining maximum nicotine for minimum tar. Approaches being used include:*
> *(a) P.E.I. treatment of filters*
> *(b) Nicotine fortification of cigarette paper*
> *(c) Addition of nicotine containing powders to tobacco*
> *(d) Alteration of blends.*[377]

Minutes from BATCO Group Research & Development Conferences in 1967 and 1969 reflect the importance of nicotine to the industry when considering product modifications to respond to concerns about smoking and health issues. Among other things, it was recommended that:

> *The development of low TPM [tar], normal nicotine cigarettes should continue. In this connection, the use of filter additives, such as PEI could be helpful in rendering the nicotine more available to the smoker.*
>
> *The development of a low TPM, low nicotine cigarette should be expanded. This raises the question of the level of nicotine required and the consumer study by*

[376f] Memorandum to T.S. Osdene from W.L. Dunn. Plans and Objectives-1979. December 6, 1978. *In* 141 Cong Rec. H7670 (daily ed. July 25, 1995).

> *[W]e will evaluate low delivery experimental cigarettes in the 5-7 mg FTC tar range but with nicotine levels which are discernibly higher than, equal to, and lower than the typical level expected of cigarettes in this range (which would be .53 mg).*

[377] Griffith RB. Report to the Executive Committee. With attached handwritten note. July 1, 1965. Page 2.

Bristol can be helpful in determining this. [It was] pointed out that there was evidence that . . . per capita cigarette consumption increased for the lower nicotine brands. It cannot, however, be assumed that the minimum nicotine offered to the smoker is the optimal level, and some consideration should be given to establishing this. [Emphasis added.][378]

Similarly, a 1975 BATCO Group Research & Development Conference report states that:

Once again the need for normal nicotine low tar cigarettes which appeal to the consumer was identified.[379] [Emphasis added.]

Another BATCO document recommended in 1976 that when tar levels are lowered, nicotine delivery should be maintained:

A second approach which could be made both with existing brands and with new brands is to aim at a lower smoke production per cigarette (i.e. lower tar) while maintaining "normal" nicotine. Work along these lines is already going on. A further modification of this approach is to maintain normal nicotine reaction for the smoker while actually reducing the total amount of nicotine per cigarette. It is believed that this can be done, e.g. by the use of P.E.I. or by alkali treatment of tobacco stems. [Emphasis added.][380]

At the 1976 BATCO "Smoking Behavior" conference it was also observed that "there would

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[378] *See:*
BATCO Group R&D Conference. Montreal, Canada. October 25, 1967. Pages 4-5.

BATCO R&D Conference. Kronberg, Germany. June 2-6, 1969.

[379] BATCO Group R&D Conference. Merano, N. Italy. April 2-8, 1975. Page 4.

See also BATCO Group Research & Development, Conference on Smoking Behavior, Southampton, UK, October 11-12, 1976. Page 8:

Provided we can get smokers to dissociate tar from nicotine in their minds in terms of a possible health hazard, then there is a clear opportunity for a range of products which at present do not exist in order to suit those who combine above average inner need [nicotine requirement - see p. 184, supra] with above average concern for health. This is very much in line with some of Russell's pronouncements, and the fact that he is advocating the 'low tar normal nicotine' cigarette fairly forcibly is something we could turn to our advantage when considering how to market such cigarettes.

[380] Morini HA. *Cigarettes with health reassurance.* BATCO Opinion. 1976. Page 1.

appear to be a forthcoming demand for high nicotine tobaccos"[381] in order to develop cigarettes that provide a higher nicotine to tar ratio.

A 1978 BATCO Group R&D Conference, which focused on product design issues, discussed several options for maintaining pharmacological satisfaction from low-tar cigarettes, including use of pharmacologically active nicotine substitutes:

> *Marketing opportunities will exist for cigarettes which are designed to replace the '1 mg cigarette.' Innovation on taste, tighter control of deliveries which may include a wider range of specified compounds, and improved control of the physical properties of the cigarette will obviously require attention. The pressure to retain smoking satisfaction may require more attention to be paid to the puff-by-puff delivery profile of the cigarette and perhaps the use of alternative active materials to augment or replace nicotine*. [Emphasis added.][382]

A 1979 BATCO R&D Policy Conference recommended continued research on aerosol growth, yet another means of reducing tar without simultaneously reducing nicotine:

> *Research on aerosol growth between inhalation and exhalation offers a way of reducing the retention of tar without at the same time reducing nicotine retention; this offers great potential to the Industry and should be continued.*[383]

A report by Imperial Tobacco Ltd. also focused on the importance of developing low-yield cigarettes that address smokers' concerns about health, but that nevertheless provide the desired "physiological satisfaction":

> *A cigarette that delivers physiological satisfaction, yet is low in T & N, must*

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[381] BATCO Conference on Smoking and Behavior, Southampton, England. October 11, 1976. Page BW-W2-02311.

[382] Green SJ. Notes on Group Research & Development Conference. Sydney, Australia. March 1978. Page 3.

[383] BATCO Notes on the R&D Policy Conference. Chewton Glen (February 10, 1979), Torquay (February 12-14, 1979). Page 4.

surely be a major objective and represents an R & D challenge.[384]

American Tobacco Company memoranda written in 1980 reveal a similar focus on increasing nicotine in relation to tar deliveries. The company conducted research on the addition of potassium carbonate to Tareyton and Pall Mall cigarettes to "increas[e] the amount of nicotine that is transferred from the tobacco to the mainstream smoke while leaving the 'tar' level unchanged."[385] One of these memoranda states that the company plans additional research on "addition of sodium carbonate, [and] treatment of stems with alkali base" with the apparent goal of "liberat[ing] nicotine as a free base . . . and thereby increas[ing] the amount of nicotine in the smoke."[386]

A large number of industry patents also demonstrate that the industry has focused substantial resources on developing methods of maintaining adequate nicotine delivery to ensure smoker satisfaction while lowering levels of other smoke constituents.[387]

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[384] Imperial Tobacco Ltd. Summary of Matinee marketing plans 1971. Page 11.

[385] *See:*
Bodenhamer NL. *Leaf Services Monthly Report for June; Increasing Nicotine Transfer in Smoke.* Memo to Dr. Eugene Glock. June 30, 1980.

Bodenhamer NL. *Leaf Services Monthly Report for August.* Memo to Dr. Eugene Glock. August 29, 1980.

[386] Memo to Dr. Eugene Glock dated July 31, 1980. Page 2. [The first page of this memo is missing from the exhibits to the Staff Report prepared by the majority Staff of the Subcommittee on Health and the Environment, 103 Cong. 2d. Sess., entitled "Evidence of Nicotine Manipulation by the American Tobacco Company" (Dec. 20, 1994).]

[387] *See, e.g.:*
U.S. Patent No. 3,584,630. Inskeep GE. *Tobacco Product Having Low Nicotine Content Associated with a Release Agent Having Nicotine Weakly Absorbed Thereon.* Philip Morris Inc. June 15, 1971. C2:5-15

U.S. Patent No. 3,861,400. Perkins PR, Bale CR. *Nicotine Fortification of Smoking Products.* Imperial Tobacco Group Limited. January 21, 1975. C1:1-10.

Industry studies on smoker compensation[388] have also led companies to be concerned that decreases in tar and nicotine yields will lead to dissatisfaction with smoking unless cigarettes are designed to allow smokers to compensate for the reduction in nicotine.[389] Consequently, tobacco manufacturers have actually attempted to assist smokers to compensate for lower nicotine yields, i.e., to obtain more nicotine from a cigarette than its machine-tested yield. They have done so by attempting to design cigarettes with "elasticity." "Elasticity" refers to the ability of a cigarette, whatever its nicotine yield as measured by a smoking machine, to deliver enough smoke to permit a smoker to obtain the nicotine he needs, e.g., through more or longer puffs or by covering ventilation holes.[390]

BATCO researchers described corporate policy on compensation and elasticity at a 1984 conference:

U.S. Patent No. 4,215,706. Larson TM, Moring TB, Ireland MS. *Nicotine Transfer Process*. Loew's Theatres, Inc. C1:40-48, C3:61-66.

U.S. Patent No. 4,236,532. Schweizer AD, et al. *Smoking Rod Wrapper*. Gallaher Limited. December 2, 1980. C1:35-40.

U.S. Patent No. 4,830,028. Lawson JW, Bullings BR, Perfetti A. *Salts Provided From Nicotine and Organic Acid as Cigarette Additives*. R.J. Reynolds Tobacco Company. May 16, 1989. C1:40-47.

[388] *See* FINDINGS § II.C.3., *supra*.

[389] *See* Adams, note 326, *supra*, at p. 108:

> *We believe in overall conclusion, that our data shows Firstly, that individual smokers adapt their smoking habit to the type of cigarette being smoked in order to try to obtain what they need from their cigarette*
>
> . . . .
>
> *Thirdly, that if because of the design of the cigarette they cannot adapt sufficiently, dissatisfaction will result.*

[390] BATCO R&D Conference. 1983. Brazil. Page BW-W2-03952: A paper on the effects of filters on cigarette smoke stated that elasticity was one of the factors that allowed a greater impression of "strength" (which is related to nicotine delivery) "within a given tar segment."

Compensation by modifying smoking regime [increasing or decreasing/puff volume, duration, puff frequency, amount inhaled] is a topic which is being explored at GR & DC and this includes designing products which aid smoker compensation.

The marketing policy concerning this type of product is not clear but it is believed it will depend largely on the degree of elasticity in the design and how overtly this elasticity is achieved. The consensus is that small improvements in elasticity which are less obvious, visually or otherwise is likely to be an acceptable route. [Emphasis added.][391]

Tobacco companies have attempted to improve elasticity through a variety of techniques. BATCO researchers noted at a 1983 conference that "elasticity can be designed into a cigarette using tobacco blend and pressure drop components. . . ."[392] Researchers at a 1972 BATCO Conference cited the need for "means of increasing the puff number of low density, low delivery cigarettes . . . in addition to those at present available."[393] At a 1975 conference, BATCO researchers were told about a German cigarette that had a number of design features that were intended to allow human smokers to obtain higher yields than the smoking machine. These design features included a higher than normal moisture content, reduced humectant, shorter cigarette rods, increased paper burn rate, additives, porous tipping, perforated tipping, acid filters, and the addition of sugars.[394]

At a 1983 BATCO R&D Conference, one of the workshops was entitled "Making the Smoke Work Harder." Notes of suggestions from that workshop include the question "What

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[391] Proceedings of the BATCO Group R&D Smoking Behaviour-Marketing Conference, Session III. July 9-12, 1984. Page 55.

[392] BATCO Smoking Behavior Conference Overview, 1983. Page BW-W2-03292.

[393] BATCO. Notes from Group R&D Conference, Chelwood; 1972. Page BW-W2-01764.

[394] BATCO Group R&D Conference, 1975, note 379, *supra,* at p. 4.

factors control human ability to change T[ar]/N[icotine] ratios?," i.e., how can a smoker, through his own behavior, alter the amount of tar and nicotine he obtains from a cigarette of a particular machine-derived yield? Many of the remaining suggestions from the workshop offer possible methods to alter the tar/nicotine ratio of a cigarette, including manipulating the pH of the smoke, and altering the ratio of free to bound nicotine. By 1984, BATCO marketing and product development personnel were recommending the use of "compensatable" filters, intended "[t]o make it easier for smokers to take what they require from a cigarette."[395]

These documents show the extent of the tobacco industry's focus on nicotine in the face of increasing pressure to alter other characteristics of their products for health reasons. The documents reveal the industry's concern with the trend toward lower-tar products, and the industry's intense preoccupation with the need to provide adequate nicotine deliveries despite lowered tar deliveries. The documents establish that the industry's rationale for seeking to provide adequate nicotine deliveries in lower-delivery products is to ensure that these low-delivery products provide smoker satisfaction. These and other documents have shown the tobacco industry's awareness that smoker satisfaction is a function of the pharmacological effects of nicotine on the brain, and the industry's keen desire to be able to offer cigarettes that will allow smokers to obtain the threshold level of nicotine necessary to experience these effects.

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[395] Structured Creativity Conference, Southampton, June 25-28, 1984. Page BW-W2-01993; attended by Ted Parrack of Brown and Williamson.

THIS SECTION OF THE DOCUMENT CONTAINS INFORMATION THAT MAY BE CONSIDERED TO BE OF A TRADE SECRET OR COMMERCIAL CONFIDENTIAL NATURE. EACH PAGE CONTAINING SUCH INFORMATION BEARS A NOTE ON THE TOP OF THE PAGE AND THE INFORMATION HAS BEEN PURGED FROM THE TEXT.

E. INDUSTRY MANIPULATION AND CONTROL OF NICOTINE DELIVERY IN MARKETED TOBACCO PRODUCTS

1. Industry Manipulation and Control of Nicotine in Cigarettes

FDA's investigation has revealed the painstaking attention that tobacco companies pay to nicotine during every phase of cigarette manufacture. This section details the methods used by the industry to manipulate nicotine delivery at each stage of production and some of the effects of these manipulations on the nicotine content (the amount of nicotine in the tobacco rod) and delivery (the amount of nicotine delivered in the smoke for absorption into the bloodstream of the smoker) of modern cigarettes.

At each step -- from tobacco growing, purchasing of tobacco leaves, and blending different types of tobacco, to cigarette design and manufacture -- ensuring adequate nicotine delivery is a central objective of cigarette manufacturers. According to a tobacco industry official:

> *Generally speaking, the nicotine yield of a cigarette is determined by the nicotine content of the tobacco; the static burn rate or amount of tobacco consumed during puffing; the pressure drop of the tobacco column; porosity of the wrapper and or ventilation at the filter; the pressure drop of the filter, the filter material, the surface area of the filter material; and the affinity of the filter material for nicotine particularly as a function of smoke pH. Through the combination of these variables, plant genetics, and commercial processes to remove nicotine from tobacco, it is possible to manipulate the yield of nicotine from about .1 mg to*

4 mg per cigarette.[395a] [Emphasis added.]

The first manufacturing step in nicotine control is the development and selection of raw materials. The tobacco industry has, through breeding and cultivation practices, developed high-nicotine tobacco plants that provide higher-potency raw material, giving manufacturers greater flexibility in blending and in providing uniform and sufficient nicotine deliveries.

Even without the selective breeding and cultivation of plants for nicotine content, careful tobacco leaf purchasing plans permit the manufacturers to control nicotine content in their products. For example, nicotine content varies among types of tobacco and from one crop year to the next. Awareness of these basic differences and monitoring of the nicotine levels in purchased tobacco allows the companies to produce cigarettes with nicotine deliveries consistent to a tenth of one percent, despite variations as high as 25% in the nicotine content of the raw material originating in the same area, from year to year.

The primary control of nicotine delivery (the amount received by the smoker), however, is in the design and careful, sophisticated manufacture of the cigarette, to ensure that the smoker obtains the precise amount of nicotine intended by the manufacturer. FDA's investigation has revealed that despite reductions in the amount of tar delivered by cigarettes over the past several decades, nicotine delivery in low-yield[396] cigarettes has not fallen proportionately with the reductions in tar. Instead, nicotine delivery has apparently risen over the last decade, a result

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[395a] Spears, AW. Lorillard Tobacco Co. *Factors Affecting Smoke Delivery of Nicotine and Carbon Monoxide.* Presented at the 1975 Symposium- Nicotine and Carbon Dioxide. November 17-18, 1975. In Symposium Proceedings-1, at p.12. FDA notes that when the author testified before Congress, he stated that nicotine manipulation does not occur and that nicotine yields simply follow tar yields. *See* note 479, *infra.* In this article he does not mention tar yield as factor in determining nicotine yield.

[396] "Low-yield" is used to denote cigarettes advertised as low-tar and low-nicotine.

that confirms that nicotine delivery is being independently and carefully manipulated by tobacco manufacturers. This newly gathered information, together with the other evidence of the industry's breeding, purchasing, blending, and manufacturing practices, reveals the extent to which manufacturers control the amount of nicotine that is delivered to the consumer from cigarettes and provides further support for the Agency's conclusion that tobacco manufacturers intend their products to affect the structure or function of the human body.

a. Tobacco Leaf Growing

The industry's control and manipulation of nicotine in the production of cigarettes begins long before the cured tobacco leaf reaches the manufacturing plant. The characteristics of leaf tobacco, including nicotine content, are established by the genetic makeup of the plant, developed during growing, and fixed by post-harvest handling. Like other raw agricultural commodities, the physical and chemical properties of tobacco, including nicotine, can vary widely, depending on genetic differences, growing season conditions, and soil type. This subsection describes the methods used by the tobacco industry to control and manipulate nicotine through careful genetic breeding and agronomic practices. As one industry expert stated, "nicotine is the key chemical constituent of the leaf and smoke and the reason for which tobacco is grown."[397]

Modern types of cultivated tobacco (*Nicotiana tabacum L*) have been selected for a relatively high level of nicotine.[398] Five major types of tobacco make up nearly all tobacco

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[397] Adapting agronomy to the needs of the low-tar era. *World Tobacco*. October 1977. Page 137.

[398] *Id.*

products marketed in the United States: Burley, flue-cured, Maryland, the Dark tobaccos, and Oriental. These tobaccos vary both in nicotine levels and in pH. The pH of a tobacco can have a significant influence on the amount of, and rate at which, nicotine is absorbed into the bloodstream of the tobacco user and delivered to the brain.

Of the five major types of tobacco, Burley tobacco generally contains the highest nicotine levels compared to other tobacco varieties, and it has an alkaline pH. Flue-cured tobacco represents the major tobacco ingredient in American cigarettes. In comparison with other tobacco varieties, flue-cured tobacco has a medium nicotine content and is somewhat acidic.[399] Maryland tobacco has a low nicotine content in comparison with other varieties and has an alkaline pH. The Dark tobaccos produce an alkaline smoke, and are the traditional tobaccos for cigar wrappers and fillers as well as for chewing tobacco and for many pipe tobacco mixtures. Oriental tobaccos, cultivated in southeastern Europe and Turkey, are used for their characteristic aroma; they have a low nicotine content, and low pH.[400]

American tobaccos of all types have undergone cumulative increases in total nicotine levels since the 1950's.[401] As the following chart demonstrates, nicotine levels in the most widely grown American tobaccos increased almost 10% for Burley and more than 50% for flue-cured between 1955 and 1980:

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[399] Browne CL. *The Design of Cigarettes*. Hoechst Celanese Corporation; 1990. Page 43.

[400] *Id.* at pp. 22, 44.

[401] DeJong DW. The role of American tobacco leaf chemistry in low-yield cigarettes: an agricultural viewpoint. *Tabak Journal International.* May 1985. Pages 376-83. DeJong notes that higher-nicotine American tobaccos are needed in limited quantities to "spike" low yield cigarette blends. He further notes that off-shore tobaccos are invariably lower in nicotine, but serve to provide "filler" style leaf materials deemed necessary for the manufacturing of low-tar cigarettes, which comprise the majority of the U.S. market.

Tobacco Type	Percent Nicotine	
	1955	1980
U.S. BURLEY	2.91	3.18
U.S. FLUE-CURED	1.93	3.07

Two tobacco industry activities over the last several decades appear to be responsible for this increase: 1) the industry's active and controlling participation in the Minimum Standards Program, which ensures that nicotine levels of U.S.-grown and marketed tobacco are maintained within specified ranges;[402] and 2) the industry's breeding and cultivation of tobacco for high nicotine levels.

The Minimum Standards Program, which began in 1963 for flue-cured tobacco and in 1977 for Burley tobacco,[403] is a component of the tobacco price-support program administered by the U.S. Department of Agriculture (USDA). With regard to domestically grown tobaccos, the industry maintains control over which varieties are suitable for growing in the United States

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[402] *Id.* at p. 382.

[403] *See:*

Letter to M. Murray, FDA, from E. Wersman, North Carolina State University, March 23, 1994, transmitting:

1) The Burley Tobacco Quality Committee-Varieties "Testing Procedure to Assure Acceptable Quality In Burly Tobacco Varieties" revised February 24, 1993.
2) The Flue-Cured Tobacco Quality Committee-Varieties "Testing Procedure to Assure Acceptable Quality In Flue-Cured Tobacco Varieties" amended January 1991.

Letter to M. Zeller, FDA, from E.M. Pfeifer, King & Spalding on behalf of the Brown and Williamson Tobacco Corp., pp.1-8, with enclosures:

Attachment 1 "Flue-Cured Tobacco Variety Committee";
Attachment 2 "Burley Variety Evaluation Committee Membership";
Attachment 3 Slides, pp. 90025-90091.

and thereby eligible for price support.

One key objective of the tobacco industry's involvement in the Minimum Standards Program appears to be to ensure that nicotine levels in marketed tobacco do not fall below specified levels. The program was initiated in response to the emergence, in the 1950's , of several so-called "discount" varieties of tobacco (e.g., "Coker 139," "Coker 187-Golden Wilt," "Coker 282," "Coker 140," "Coker 316," and "Reams 64") that failed to meet current industry specifications established, among other things, to control the amount of nicotine delivery when used in manufacturing filtered cigarettes. To insure the elimination of "discount" or low-nicotine varieties from the market, the industry obtained the necessary cooperation from USDA to eliminate these varieties from the price-support program. In fact, to be eligible under this program, growers must certify, even to this day, that "discount" varieties are not being grown.[404]

In 1979, one major U.S. manufacturer requested that the tobacco variety committee under the Minimum Standards Program lower the acceptable nicotine range, established in 1967, for the specific tobacco varieties used as the standard. Support for lowering the acceptable nicotine range was not forthcoming from the rest of the industry and the change was never adopted.[405] In fact, in spite of the trend toward marketing cigarettes advertised as low delivery, the criteria under the Minimum Standards Program for nicotine content of new varieties have not changed since 1967.

While the Minimum Standards Program ensured that nicotine levels in marketed tobaccos

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[404] USDA Agricultural Stabilization and Conservation Service (ASCS) Manual. "Identification of certain flue-cured tobacco varieties under the price support program." April, 1964. Pages 3-5, 8, 10-11. Obtained on June 15, 1994, from USDA-ARS-SAA, Crops Research Laboratory.

[405] Collins WK. Cultural practices increase nicotine content of U.S. flue-cured leaf. *Tabak Journal International.* [4] 1981:328, 330.

did not fall, breeding and cultivation initiatives undertaken by the industry caused nicotine levels to increase. When health concerns prompted the tobacco industry to begin to market low-tar cigarettes in the 1960's and 70's, the industry turned to tobacco breeders to develop tobacco varieties that produced less tar. Breeders found that without intervention in the breeding of these varieties, nicotine levels were reduced along with tars.[406] Thus, the industry has long been able to grow low-tar and low-nicotine varieties of tobacco for use in manufacturing cigarettes.

By 1978, however, the industry had abandoned its interest in the development of low-tar/low-nicotine varieties of tobacco for manufacturing low-yield cigarettes, and instead turned to the development of higher nicotine varieties. According to one expert in the field, it was necessary to focus on developing tobacco that was higher in nicotine, not lower:

> *. . . manufacturers have means of reducing tars but most of the methods reduce nicotine and other constituents at the same time. Therefore it may be desirable to develop levels constant or to develop lines higher in nicotine so that when the tar and nicotine are reduced there will still be enough nicotine left to satisfy the smoker.*[407] [Emphasis added.]

Industry experts agreed, stating in 1981 that the nicotine content of tobacco "will increase if the very low 'tar' brands continue to expand in market share,"[408] They further stated that:

> *[c]urrent research is directed toward increasing the nicotine levels while maintaining or marginally reducing the 'tar' deliveries.*[409]

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[406] Tailoring tobacco plants to meet future demands. *World Tobacco*. October 1978. Page 148. Abbreviation of talk by J.F. Chaplin at meeting of CORESTA scientists in Sofia, Bulgaria.

[407] *Id.*

[408] Spears AW, Jones ST. Chemical and physical criteria for tobacco leaf of modern day cigarettes. *Recent Advances in Tobacco Science.* 1981;7:19-39, 37.

[409] *Id* at p. 31. *See* DeJong, note 401, *supra,* at p. 378. In anticipation of a move toward low-yield cigarettes, USDA was once petitioned by the industry to promulgate regulations to allow for the growing of ultra-low nicotine tobacco. The regulations were actually published in the *Federal Register* in June 1947. The nicotine concentration was to be no higher than 0.8%, which is significantly lower than the

The industry has elsewhere acknowledged that the role of American tobacco is to provide high levels of nicotine in the finished product to offset the diluting effect of bland foreign tobaccos and reconstituted tobacco sheet.[410]

FDA's investigation has revealed that at least one cigarette manufacturer, Brown and Williamson, has developed and marketed a tobacco so high in nicotine that it exceeded the limits imposed for U.S.-grown tobacco under the Minimum Standards Program. These limits cannot be exceeded without significant risk of losing government-administered price support. However, foreign-grown tobaccos are not subject to these specifications and are not subject to testing for nicotine content upon entry into the United States. This high-nicotine tobacco was therefore grown in South America.

FDA found that Brown and Williamson was involved for more than a decade in developing, through a combination of conventional and advanced genetic breeding techniques, a high-nicotine, flue-cured tobacco plant, named "Y-1," for use in a number of low-tar brands of cigarettes in the United States.

Brown and Williamson characterized its achievement in a patent filing in the following way:

> *By the present invention or discovery, applicants have succeeded in developing a tobacco plant that is agronomically and morphologically suitable for commercial tobacco production, i.e. it closely resembles SC 58, and provides a pleasant taste and aroma when included in smoking tobacco products, yet it is possessed of the N. rustica high-nicotine attribute. So far as we know, this has not been*

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concentration of nicotine in domestic tobaccos. These low-nicotine varieties were to be kept entirely separate and marketed under contract. These regulations remain in the Code of Federal Regulations (7 CFR 30), but they have never been taken advantage of, indicating industry's lack of interest in the development of ultra-low nicotine tobaccos.

[410] *See* DeJong, note 401, *supra.*

accomplished before . . . [Emphasis in original.] [411]

The development of Y-1 dates back to at least the mid-1970's. In 1977, James F. Chaplin, who was affiliated with both USDA and North Carolina State University, indicated that tobacco could be bred to increase nicotine levels, by crossbreeding commercial varieties of tobacco with *Nicotiana rustica. N. rustica* is a wild tobacco variety that is very high in nicotine, but is not used in manufacturing cigarettes because of its harshness.[412]

By combining conventional and advanced breeding techniques, Brown and Williamson succeeded in developing commercially viable Y-1 from seeds initially produced by Chaplin's crossbreeding work. The nicotine content of the leaf of this variety is about 6% by weight, which is higher than that of any other varieties of tobacco commercially grown in the United States. (Domestically grown varieties of flue-cured tobacco, for example, naturally contain 2.5% to 3.5% nicotine.[413])

Company officials admitted to FDA that Y-1 was intended as a "blending tool" to enable the company to design products that were lower in tar but not lower in nicotine.[414] The company disclosed to FDA that Y-1 had been used commercially in the manufacturing of Viceroy King Size, Viceroy Lights King Size, Richland King Size, and Richland Lights King Size and it

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[411] U.S. patent application No. 761,312 submitted on September 17, 1991.

[412] Chaplin JF. *Breeding for varying levels of nicotine in tobacco.* Proceedings from a symposium on Recent Advances in the Chemical Composition of Tobacco and Tobacco Smoke. 1977. Page 334.

[413] Letter to D.A. Kessler, FDA, from J. W. Johnston, R.J. Reynolds Tobacco Co. February 28, 1994. Pages 1-2.

[414] Transcript of FDA meeting with Brown and Williamson. June 17, 1994. Pages 18, 29, 85-86, 124.

constituted about 10% of the tobacco blend of these products.[415] These brands were manufactured and distributed throughout the United States in 1993.[416] FDA's investigation revealed that, as of mid-1994, Brown and Williamson still had between 3.5 million and 4 million pounds of this high-nicotine tobacco on hand.[417]

In addition to breeding high-nicotine tobacco varieties, the tobacco industry engages in a number of agronomic practices that increase nicotine levels in tobacco. Heavy application of nitrogen fertilizers, early topping, and tight "sucker" (i.e., bud growth at the junction of stalk and leaves) control have all acted in concert to push nicotine levels upward.[418] In addition, tobacco varieties have been selected for tolerance to brown spot, a leaf disease that makes early harvest necessary. Leaves of disease-resistant varieties tend to remain in the field longer, resulting in maximum nicotine accumulation.[419] Since the introduction in 1965 of the acreage-poundage control system, farmers have reduced the number of harvestable leaves per plant and have tended to increase plant spacing. Both of these practices tend to increase nicotine content in the leaf.[420] Finally, tobacco growers are transplanting tobacco crops earlier, which, coupled with the widespread use of pesticides in the soil, often results in slow early season growth, and also tends

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[415] *Id.* at pp. 153, 165.

[416] *Regulation of Nicotine under the Federal Food, Drug, and Cosmetic Act: hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives,* 103 Cong. 2d Sess. (June 21, 1994)(statement of David A. Kessler, M.D., Commissioner of Food and Drugs, "The Control and Manipulation of Nicotine in Cigarettes," at pp. 9-12). The Commissioner's statement is included as Appendix 8 to this document.

[417] *See* Transcript, note 414, *supra,* at p. 124.

[418] *See* DeJong, note 401, *supra,* at p. 382.

[419] *See* Collins, note 405, *supra,* at p. 330.

[420] *Id.*

to increase nicotine content in the leaves.[421]

These nicotine-raising agronomic practices have been adopted by U.S. growers in recent years, even though over 50% of the U.S. cigarette market is now characterized as low delivery. Thus, the tobacco industry has developed a number of sophisticated methods for manipulating nicotine levels through breeding and cultivation of tobacco plants and has used these methods to maintain and increase concentrations of nicotine in tobacco leaves. These methods enable the industry to use high-nicotine leaf in low-tar cigarettes, so that, paradoxically, certain low-tar cigarettes now contain more of the higher nicotine tobacco in their blend than cigarettes with higher tar deliveries.[422] See p. 261 infra. The use of these methods demonstrates that the industry manipulates nicotine independently of other tobacco components to ensure that cigarettes contain sufficient nicotine to satisfy smokers.

b. Leaf Purchasing

Nicotine is perhaps the most important criterion employed by cigarette companies in the purchase of tobacco leaf. As one tobacco company official stated over 20 years ago in an industry publication:

> *It is believed that one important reason why the consumer smokes cigarettes is for the nicotine which they contain . . . Manufacturers, therefore, must have all options open in selecting leaf to buy.*
>
> *They are most concerned with the nicotine levels in leaf, so that after manufacture of their blends, the nicotine percentages in the cigarettes will vary minimally both*

[421] *See* Collins, note 405, *supra.*

[422] *See* Spears, note 408, *supra,* at p. 22.

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from one to another within a packet, and from packet to packet.[423] [Emphasis added.]

The key factor related to nicotine in leaf purchasing is stalk position. The concentration of nicotine is lowest at the bottom of the plant and highest in the top leaves of flue-cured tobacco.[424] Thus, the position of the leaf on the stalk determines how much nicotine the leaf will contain. In fact, "stalk position" is an industry euphemism for nicotine content. The stalk position of a leaf can be determined by its appearance, shape, color, and thickness, even after harvest.[425] Therefore, an experienced buyer, whose instructions are dictated by the manufacturer's chemists,[426] need only be concerned with these physical characteristics in identifying leaves of varying nicotine content.

The significance of stalk position in leaf purchasing was confirmed when FDA visited cigarette manufacturers. [redacted] [427]

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[423] What changing technology means for leaf producers and packers. *World Tobacco*. September 1971. Page 137. Based upon lecture by J.S. Campbell, American Organisation of the Imperial Tobacco Group Ltd. at a Conference on Social and Economic Issues Confronting the Tobacco Industry in the Seventies, Lexington, KY.

[424] *See* 1977 *World Tobacco* article, note 397, *supra*. *See also* Browne, note 399, *supra*, at p. 15.

[425] *See* 1977 *World Tobacco* article, note 397, *supra*.

[426] Evolving techniques of making cigarettes milder. *World Tobacco*. April 1979. Page 95.

[427] FDA officials Mitch Zeller, Kevin Budich, Barbara Frazier, and Bob Spiller visited the sites of R.J. Reynolds Tobacco Company on April 11-12, 1994, and Brown and Williamson Tobacco Company on May 3, 1994. The following references refer to their summary notes of the visits.

Zeller notes from RJR visit at p. 2.
Budich notes from RJR visit at p. 3.

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Furthermore, this RJR representative revealed that "impact" is a criterion in leaf purchasing and that "impact" is "basically a function of nicotine in tobacco."[428] RJR also indicated that "impact" is measured in the company's laboratories if there is enough time to do so prior to purchase.[429]

Representatives from Brown and Williamson also described the significant role that nicotine plays in the purchase of tobacco leaf. The company stated that stalk position is the "first thing" they look for during leaf purchasing.[430] At Brown and Williamson, the lower stalk positions are considered to have the least amount of "smoke quality," which was defined as including "impact level."[431] The company defines "impact" as "the hit or punch in the back of the throat when you first inhale."[432]

Nicotine levels are so crucial to leaf purchasing at Brown and Williamson that the

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[428] Zeller notes from RJR visit at p. 2.
Budich notes from RJR visit at p. 3.
Frazier notes from RJR visit at p. 2.
RJR overhead was provided at visit.

[429] Zeller notes from RJR visit at p. 2. [redacted]

[430] Zeller notes from B&W visit at p. 2.
Frazier notes from B&W visit at p. 2.
Spiller notes from B&W visit at p. 2.

[431] Zeller notes from B&W visit at p. 2.

[432] Zeller notes from B&W visit at p. 2.
Budich notes from B&W visit at p. 4.
Frazier notes from B&W visit at p. 2.
Spiller notes from B&W visit at p. 2.

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company actually adjusts the stalk positions of its leaf purchases based upon the results of nicotine analyses that are performed during the course of the buying season.[433] In addition, Brown and Williamson employs special measures when purchasing foreign tobacco to ensure adequate nicotine levels. The company stated that foreign Burley and flue-cured tobaccos are smoked prior to their purchase so that they get some sense of the "impact" of the tobacco,[434]

[redacted][435]

c. Leaf Blending

After purchase, tobacco leaves are blended to attain target levels of nicotine and tar in the smoke. FDA's investigation noted particular attention on the part of manufacturers to the nicotine content of the leaf in the blending operation. As noted above, blending practices by manufacturers are designed to: (1) control the naturally occurring variations in nicotine and other components caused by genetics, growing season conditions, and soil type within a given type and grade; and (2) particularly for low-tar cigarettes, to increase nicotine concentrations and thereby maintain an acceptable nicotine level in the cigarettes.

As described above, each type of tobacco has unique characteristics of nicotine and tar delivery. Moreover, within each type, levels of nicotine increase with ascending stalk position

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[433] Frazier notes from B&W visit at p. 2.

[434] Spiller notes from B&W visit at p. 2.
Frazier notes from B&W visit at p. 2.

[435] [redacted]

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(grade). Armed with this knowledge, tobacco manufacturers blend various types of tobaccos and various stalk positions to achieve specific nicotine levels in particular brands.

Manufacturers also pay attention to other features of tobaccos that can affect nicotine delivery during blending. For example, cigarette filling power (bulk), pressure drop or resistance to draw, and static burn rate are all decreased with ascending stalk position. Decreases in burn rate increase the puff count, and thereby result in the delivery of more nicotine to the smoker because less tobacco is burned between puffs.[436]

The pH of cigarette smoke directly affects the delivery of nicotine because it alters the amount of nicotine that is absorbed in the mouth or lungs.[437] PH is controlled by the manufacturer in the selection of the type of tobacco used and blended. For example, smoke-condensate pH is higher from certain tobacco varieties as well as from leaves at upper stalk positions.

Blending techniques have been used to finely control nicotine concentrations in marketed cigarettes. [redacted][438] This is a high

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[436] *See* Browne, note 399, *supra,* at p. 12.

[437] *See* Surgeon General's Report. *Nicotine Addiction.* 1988. Pages 29-31.

[438] [redacted]

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degree of control even in a product manufactured from synthetic, homogeneous materials. It is a remarkable degree of control for a product such as cigarettes, which are made from highly variable biological materials whose nicotine content is ordinarily dependent upon such uncontrollable factors as weather and plant attack by insects and plant diseases.

Significant evidence also demonstrates that tobacco manufacturers have used blending techniques to increase nicotine concentrations in low-tar cigarettes and thereby maintain nicotine delivery while reducing tar delivery. FDA has observed the industry's use of proportionately greater amounts of higher nicotine-containing Burley tobacco in the tobacco blends of the lowest-tar varieties of cigarettes. In fact, Thomas Sandefur, the chief executive officer of Brown and Williamson, admitted to Congress that nicotine levels can be adjusted "up or down" depending on the blend of tobaccos used in a particular cigarette.[439] Industry scientists have also acknowledged that tobacco manufacturers blend high-nicotine tobaccos to compensate for the reductions in nicotine caused by innovations in cigarette design and manufacturing to reduce tar deliveries.[440]

[redacted]

[redacted]

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[439] *Regulation of Nicotine under the Federal Food, Drug, and Cosmetic Act: hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives,* 103 Cong. 2d Sess. (June 23, 1994) (testimony of Thomas E. Sandefur, Jr., CEO, Brown and Williamson Corp., transcript at p.133).

[440] *See:*
DeJong, note 401, *supra.*

Spears, note 408, *supra,* at pages 22-24.

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[redacted] These examples demonstrate that tobacco manufacturers deliberately increase the proportion of high-nicotine tobaccos in low-tar cigarettes to prevent reductions in nicotine delivery that would otherwise result in these products.

Moreover, as described above, Brown and Williamson developed "Y-1," its ultra-high nicotine tobacco, for the purpose of having a "blending tool" that could be used to maintain nicotine delivery while reducing tar.

d. Cigarette Design and Manufacture

Cigarettes are not simply cut tobacco rolled into a paper tube. Modern cigarettes, as sold in the United States, are painstakingly designed and manufactured to control the amount of nicotine delivered to the smoker. The following aspects of cigarette design and manufacturing all affect the nicotine delivery of a finished cigarette:

(i) the chemical manipulation of tobacco smoke;

(ii) the use of flavors and casings;

(iii) filtration;

[441] Zeller M, Budich K. Notes from March 22-23, 1994 meeting with Philip Morris and April 10-12, 1994, meeting with RJR. Mitch Zeller's notes, at pp. 2-3, and Kevin Budich's notes at p. 9.

(iv) the use of reconstituted tobacco; and

(v) use of wider tipping paper.

(i) Chemical Manipulation

Tobacco manufacturers add certain chemicals to the tobacco to enhance the efficient extraction by the smoker of nicotine from the tobacco in the rod. For example, certain additives can alter the pH of cigarette smoke, which is known to affect the rate of absorption of nicotine into the bloodstream of the smoker.[442]

FDA's investigation has disclosed efforts by the industry to chemically enhance nicotine delivery. A major American tobacco company's 1991 handbook on leaf blending and product development shows that ammonia from such sources as diammonium phosphate (DAP),[443] ammonium hydroxide, and urea can be used in cigarette manufacturing to increase the amount of nicotine delivered to the smoker.

The handbook states that ammonia in cigarette smoke:

> *can liberate free nicotine from the blend, which is associated with increases in impact and 'satisfaction' reported by smokers.*[444]

The handbook goes on to describe ammonia as an "impact booster":

> *Ammonia, when added to a tobacco blend, reacts with the indigenous nicotine salts and liberates free nicotine. As a result of such change, the ratio of extractable nicotine to bound nicotine in the smoke may be altered in favor of extractable nicotine. As we know, extractable nicotine contributes to impact in*

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[442] Surgeon General's Report. *Nicotine Addiction.* 1988. Pages 29-31.

[443] *See* Statement of David A. Kessler, note 416, *supra,* at pp. 9-12.

[444] *Id.* at p. 10.

cigarette smoke and this is how ammonia can act as an impact booster.[445]

Ammonia increases the pH of the smoke and thereby enhances the absorption of nicotine by the body.[446] FDA's investigation has revealed at least one common site for the application of ammonia and ammonia-like compounds: reconstituted tobacco. The agency has found levels of these compounds to be as high as 10 % in reconstituted tobacco.

The company handbook describes the benefits of the treated reconstituted tobacco as a source of ammonia to absorb nicotine from higher alkaloid-containing components in the blend. This company handbook also describes the application of ammonia directly to the leaf tobacco.

With regard to the question of the efficiency of this technology in increasing nicotine delivery, the handbook states that smoke analysis shows that an experimental cigarette made of reconstituted tobacco treated with ammonia has almost double the nicotine transfer efficiency of tobacco.[447] This handbook also states that many U.S. tobacco manufacturers utilize ammonia technology. One company has admitted to FDA that it uses DAP in manufacturing cigarettes, and that such use increases nicotine delivery.[448]

(ii) Flavors and Casings

Various substances are added to tobacco components to affect the flavor and palatability of smoke, alter smoke composition and yield, modify burn rate, and alter pH to optimize nicotine

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[445] *Id.*

[446] Surgeon General's Report. *Nicotine Addiction.* 1988. Pages 29-31.

[447] *See* Statement of David A. Kessler, note 416, *supra,* at pp. 10-12.

[448] *See* King and Spalding letter, note 403, *supra,* at p. 6.

delivery. According to one industry expert,[449] the major contribution of the tobacco flavor specialist is to:

> *help provide a rich, clean, full-bodied tobacco flavour, to keep to a minimum hotness and irritation in the mouth, and to ensure high satisfaction from an adequate level of nicotine per puff. . . requirements that guarantee the consumer a pleasurable smoke . . .*

So-called "casings" are solutions of usually water-soluble ingredients that provide a means of incorporating flavorings and other additives into the tobacco blend. Casings are often used in tobacco processing to reduce the harshness of nicotine in high-nicotine tobaccos, thus permitting greater use of these tobaccos in cigarette manufacture. This use of casings is described by an industry "flavorist" in the following quote:

> *It is assumed that nicotine is one of the primary satisfaction factors for which tobacco products are used. However, in air-cured tobaccos (cigar, burley, Maryland), the pH of the smoke is generally alkaline and the flavor effect of nicotine is a "harshness" which can be choking and unpleasant. In the case of tobaccos containing sugars (flue-cured, oriental), the tobacco is weakly acidic, the effect of the nicotine is greatly modified, and the harshness is dramatically reduced. This same effect is often achieved by addition of sugars to air-cured tobaccos to "mellow" the smoke and/or by the blending of air-cured tobaccos with flue-cured and oriental. [Citation omitted.] Thus, smoke pH and leaf sugar content are factors which play an important role in the nicotine strength perceived in the smoking process.*[450]

As is clear from this quote, casings are used to permit the incorporation of high-nicotine tobaccos in cigarette blends, despite their unpleasant taste. Casings composed of such additives as sugar, licorice, or cocoa help to overcome the bitterness of nicotine in smoke. The lengths to which tobacco manufacturers go to use high-nicotine tobaccos, despite the harsh taste of

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[449] Hertz AN. The flavourist's role in the cigarette design team. *World Tobacco.* March 1985. Page 97.

[450] Leffingwell JC. Nitrogen components of leaf and their relationship to smoking quality and aroma. *Recent Advances in Tobacco Science.* Volume 2. Page 9.

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nicotine, reveals that the nicotine in these tobaccos is not being used for its taste but for another purpose.

FDA's investigation revealed the following example of the application of casings to permit a use of a high-nicotine tobacco that would otherwise have been unpalatable to consumers. [redacted][451]

Manufacturers also reduce harshness by routinely adding acids to tobacco to lower the pH of the smoke.[452] Manufacturers also use conventional casing materials, such as sugars and cocoa, to produce acids in the smoke and reduce harshness.[453] Harshness from nicotine is also reduced by spraying on top dressings after the tobacco is cut and shredded for cigarette making.[454]

Casings often include a humectant, usually glycerine or a higher glycol, which serves to

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[451] [redacted]

[452] *See* King and Spalding letter, note 403, *supra,* at p. 6.

[453] *Id.*

[454] *Id.*

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keep the tobacco moist and less sensitive to changes in humidity.[455] RJR acknowledged using glycerine as a humectant.[456] Tobacco industry officials acknowledge that controlling moisture content is essential to ensure that nicotine content does not fall.[457] Humectants also act to control particle size in the formation of the smoke aerosol, making the smoke "smoother" or less harsh on the back of the throat. Smoother smoke facilitates inhalation, ensuring that the nicotine will be taken into the lungs and rapidly and completely absorbed.

Nicotine can also be added to cigarettes through application of tobacco extracts in the processing of tobacco. Although calling the contribution of flavored tobacco extracts to the overall nicotine delivery from cigarettes "trivial," tobacco companies admitted to having used such extracts in testimony before Congress,[458] in other public statements,[459] [redacted]

[redacted]

[redacted]

[redacted]

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[455] *See* Browne, note 399, *supra,* at pp. 55-56.

[456] Budich K. Notes from April 10-12, 1994, meeting with RJR. Page 8.

[457] DeBardeleben MZ, Clafin WE, Gannon WF. (Philip Morris Research Center). Role of cigarette physical characteristics on smoke composition. *Recent Advances in Tobacco Science.* Volume 4. Page 98 ("Nicotine decreases on a per puff basis as moisture content increases . . . . The decrease is dramatic as moisture content rises above 12%").

[458] *Regulation of Tobacco Products (Part I): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives,* 103 Cong. 2d Sess. 592, 596 (April 14, 1994) (testimony of Edward A. Horrigan, Jr., Liggett Group, Inc. and Andrew Tisch, Lorillard Tobacco Co.).

[459] Philip Morris press release. *Philip Morris Statement on Nicotine in Cigarettes.* March 25, 1994. Page 2.

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[redacted][460]

(iii) Filtration

The filter plug provides a mouthpiece that captures particulate matter from the smoke and absorbs vapors. The filter can be used as a vehicle to carry filter aids such as charcoal and other solids and liquid additives that permit selective filtration of certain chemicals. The manufacturer's selection of a particular filter is determined largely by the target levels of nicotine and tar.[461]

Significant research has been conducted by the tobacco industry on the use of filter additives to enhance nicotine delivery.[462] FDA's investigation revealed that at least one major cigarette manufacturer has added a chemical to the filters used on its marketed cigarettes that increases the amount of nicotine delivered to smokers, by increasing the amount of nicotine that is eluted from the filter. "Elution" is the process by which nicotine that is initially trapped on a

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[460] *See:*

Hunter J. FDA memo to the record. Conversation with Steve Block of IFF. March 23, 1994.

Layloff T, FDA. Memo to James Hunter, FDA. Tobacco Extract Analyses. February 24, 1995.

[redacted] The actual contribution of tobacco extracts to total nicotine delivered to the smoker by tobacco so treated is unclear. The industry has conducted research to examine the specific activity of added versus naturally occurring nicotine. *See* Jenkins RW, Comes RA. Exogenous vs Endogenous Transfer of Nicotine During Smoking. *Int. J. Appl. Radiat. Isotopes.* 1976;27:323-324.

[461] *See* Browne, note 399, *supra,* at p. 66.

[462] Reynolds ML. Influence of filter additives on smoke composition. Page 54. Undated.

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filter is remobilized into the mainstream smoke by hot vapors and becomes available for inhalation by the smoker. [redacted][463]

Filter ventilation, which is accomplished by making holes in the filter wrap and tipping paper, is also a major means of controlling the nicotine delivery of a cigarette. Ventilation has apparently now largely replaced interest in filter additives as a means of enhancing nicotine delivery.[464] Ventilation holes allow fresh air to be pulled in by the smoker's suction, thereby diluting the smoke. Ventilation does not, however, simply reduce the concentration of each smoke component in proportion to the degree of dilution. Instead (while ventilation does reduce the tar and nicotine deliveries compared to a non-ventilated cigarette), ventilation can be used to increase the proportion of nicotine compared to tar.[465]

Tobacco manufacturers control filter ventilation by (1) changing the number and location

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[463] [redacted]

[464] *See* Reynolds, note 462, *supra,* at p. 61.

[465] Kiefer JE. Ventilated Filters and their Effect on Smoke Composition. In: *Recent Advances in Tobacco Science.* Volume 4. Physical Parameters which Affect the Composition of Cigarette Smoke from 32nd Tobacco Chemists Research Conference. October 30 - November 1, 1978. Montreal, Canada. Pages 78,79.

of holes in the filter tipping paper, which surrounds the filter at the smoker's end of the cigarette rod; and (2) by controlling the porosity of the plug wrap, which underlies the tipping paper and surrounds the filter.[466]

As the amount of ventilation increases, the amount of tar and nicotine are not proportionately reduced. Instead, tar is reduced at a greater rate than nicotine, thereby increasing the proportion of nicotine to tar. For instance in one reported measurement, as the proportion of filter ventilation went from 0% to 50%, mainstream smoke tar dropped 47% (29.38 to 15.71 mg/cigarette), while mainstream smoke nicotine dropped 37% (1.70 to 1.07 mg/cigarette).[467] The effect of using such ventilation is that the manufacturer has selectively reduced tar while delivering a higher percentage of the available nicotine to the smoker.

Filter ventilation can produce low nicotine and tar delivery ratings when measured by the FTC smoking machine, yet still manage to deliver higher nicotine levels to the smoker than indicated by the FTC yield. Research has shown that, unlike the FTC smoking machine, 32% to 69% of low-tar cigarette smokers block the perforations in ventilated filters with their fingers or lips. This behavior is not unexpected because some smokers are unaware of these ventilation holes or their function, and because the holes are generally tiny, laser-generated perforations and difficult for the smoker to see. Blockage of these holes results in greater nicotine yields to the smoker than those measured by the FTC smoking machine.[468] This filter design provides a

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[466] *See* Browne, note 399, *supra,* at p. 10.

[467] *See* Browne, note 399, *supra,* at p. 84.

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

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means of compensating for reductions in nicotine delivery that are produced by unblocked filter ventilation. The ability to block ventilation holes is thus a means of improving a cigarette's "elasticity," i.e., a design feature that allows smokers to "compensate" for nicotine losses that would otherwise be caused by tar-reducing modifications. See p. 229, supra.

Another ingenious compensatory method to boost nicotine delivery has been the development of the so-called channel-ventilated filter system. This system has been employed by Brown and Williamson for its BARCLAY brand launched in 1981, and represents an attempt to avoid some of the reduction in nicotine that can accompany the use of ventilated conventional filters. The channel-ventilated filter functioned differently when tested on the FTC smoking machine than when used by humans. In fact, in an investigation that commenced in 1981, the FTC found that air flow through these channels is indeed compromised during actual smoking and that BARCLAY's channel filter actually delivers considerably more nicotine and tar to the smoker than is obtained using the FTC's testing method.[469] In 1983, the FTC successfully sued to enjoin Brown and Williamson from using nicotine, tar, and carbon monoxide results obtained from the FTC's smoking machine testing method in its BARCLAY advertising.[470] [redacted]

[469] Federal Trade Commission. "Report to Congress Pursuant to the Federal Cigarette Labeling and Advertising Act," for the year 1981(July 1984) and 1984(1986).

[470] FTC v. Brown & Williamson Tobacco Corp., 580 F. Supp. 981, 983, 987, n. 35, and 988 (D.D.C.1983), aff'd in part (affirmed holding that the 1 mg tar claim had a tendency to deceive) and remanded in part, 778 F. 2d 35 (D.C. Cir. 1985). RJR and Philip Morris had complained to the F.T.C. that Brown and Williamson's Barclay advertisement claim of 1 mg tar was inaccurate and misleading, and that "when the cigarette is smoked between human lips its air ventilation system is inevitably obstructed and the cigarette delivers disproportionately more tar and nicotine than other comparably rated cigarettes." 778 F.2d at 37. Brown and Williamson argued, among other things, that Barclay had a higher ratio of nicotine to tar. 580 F. Supp. at 981, 984.

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[redacted] [471]

(iv) Reconstituted Tobacco

Cigarette manufacturers claim that the development and use of reconstituted tobacco sheet represents a cost-cutting measure to minimize tobacco waste. But the role of reconstituted tobacco in reducing tar and in controlling nicotine delivery is also apparent. The first use of reconstituted tobacco occurred in the 1950's by RJR, primarily as a method for reducing tar, in WINSTON cigarettes.[472] RJR estimates that reconstituted tobacco is used in virtually every cigarette brand on the market.[473] U.S. manufacturers generally use between 20% and 25% of this material.[474]

In the reconstitution process, pieces of tobacco material undergo treatment that results in the extraction of some soluble components, including nicotine. The pieces are then physically formed into a sheet of tobacco material, to which the extracted nicotine is re-added. Even if this

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[471] Budich K. Notes from May 3, 1994, meeting with Brown and Williamson. Page 12.

Federal Trade Commission. "Tar, Nicotine, and Carbon Monoxide of the Smoke of 933 Varieties of Domestic Cigarettes." 1994. Pages 9-10.

[472] Chemical and Biological Studies On New Cigarette Prototypes That Heat Instead of Burn Tobacco, R.J. Reynolds Tobacco Co. Winston-Salem, NC. 1988. Page 29. By increasing the use of reconstituted tobacco sheet in the cigarette rod (thereby reducing the amount of cut tobacco leaf needed) and using increasingly more efficient filtration, the levels of tar have been further reduced by the industry since the 1950's.

[473] *Id.*

[474] *See* Browne, note 399, *supra,* at p. 47.

reconstituted material contains only the original nicotine, its recombination with the tobacco material may be viewed as adding nicotine to the cigarette because the nicotine had been removed. Although denied by tobacco executives,[475] it is publicly reported that this process adjusts nicotine levels in the products, and that one manufacturer "readily admits to setting levels of nicotine . . . for the tobacco sheet."[476]

The agency has observed that the primary methods of producing reconstituted tobacco sheet are closely monitored and controlled to preserve the amount of nicotine in the tobacco components. These processes enable the manufacturer to precisely control and evenly disperse nicotine throughout this material, bringing a high degree of uniformity and consistency to the composition of a raw agricultural commodity. This control is so refined that despite the wide variability in the nicotine content of unprocessed tobaccos, reconstituted tobacco contains a generally uniform concentration of nicotine of around 1%, industry-wide. And, as described below, the reconstitution process can actually be used to elevate the level of available nicotine.

At least one company, LTR Industries, LeMans, France, which is involved exclusively in the production of reconstituted tobacco sheet for the cigarette industry, has publicly acknowledged the extent to which the production of such material can be controlled to precisely affect nicotine and tar deliveries.

According to an article appearing in the February 1983 issue of Tobacco Journal International, LTR claims that its process can produce reconstituted tobacco sheet to satisfy any

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[475] *Regulation of Tobacco Products (Part I): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representaives,* 103 Cong. 2d Sess. 543 (April 14, 1994) (testimony of William I. Campbell, President and CEO, Philip Morris U.S.A.).

[476] Sisele S. Tobacco scrap: cigarette makers are taking heat for adjusting nicotine levels. *The Charlotte Observer.* March 6, 1994. Page 1C.

manufacturer's specifications for nicotine delivery. In this article, LTR states that "based on the idea that reconstituted tobacco could be used as a nicotine regulator, we have developed products with reduced or fortified nicotine." LTR has also been identified as having the ability to manipulate nicotine levels in reconstituted tobacco either by working into the scrap and waste new nicotine-rich tobacco of the "*rustica* type," or by adding purified salts of nicotine into the slurry, to boost the levels of nicotine in the finished reconstituted tobacco sheet.[477]

(v) Use of Wider Tipping Paper

Another means to compensate for nicotine losses from tar-reducing design options is the industry's use of wider tipping paper overwrap. According to a study conducted by Grunberg et al.,[478] between 1967 and 1978, the width of the overwrap was increased on 18 brands of filter cigarettes, even though there was smokable tobacco under the widened overwrap. The Grunberg study found that the wider tipping paper reduced the amount of tobacco smoked during the FTC testing method, because the FTC method prescribes that cigarettes be smoked down to within 3 millimeters of the tipping paper rather than until all of the tobacco is burned. Thus, use of wider tipping paper causes a decrease in the FTC yields of tar and nicotine while permitting smokers to obtain a higher yield of both tar and nicotine from the cigarette. Like the use of ventilation holes, use of wider tipping paper constitutes a form of built-in "elasticity" because it increases the amount of nicotine a smoker can obtain from a cigarette over the advertised FTC yield.

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[477] Evolving techniques of making cigarettes milder. *World Tobacco.* April 1979. Pages 93-101.

[478] Grunberg NE, Morse DE, Maycock VA, Kozlowski LT. Changes in overwrap and butt length of American filter cigarettes. *NY State Journal of Medicine.* July 1985. Pages 310-312.

e. Manipulation of Nicotine in Low-Yield Cigarettes

The manipulation and control of nicotine in cigarette design and manufacture is particularly apparent when low-yield cigarettes are analyzed. Since the genesis of the low-tar cigarette, the industry has recognized that the use of tar-reducing modifications, such as those described above, can reduce nicotine delivery. This has led some manufacturers to compensate for the effects of tar reduction to ensure an adequate delivery of nicotine in the low-yield products.[479] As one article in a 1979 industry publication states, the current practice is "to prefer tobaccos rich in flavour elements, even though that may mean their having more nicotine and tar than is desirable, and seeking to reduce the latter without doing too much harm to the former."[480]

To a remarkable degree, the cigarette industry has accomplished the task of maintaining delivery of nicotine while decreasing tar in low-tar products. In 1988, Jacob et al.[481] found that,

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[479] The tobacco industry has repeatedly stated that reductions in tar yields result in proportionate reductions in nicotine yields. *See, e.g. Regulation of Tobacco Products (Part I): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives,* 103rd Cong., 2d Sess. 363 (1994) (statement of R. J. Reynolds Tobacco Company); *Regulation of Tobacco Products (Part I): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives,* 103rd Cong., 2d Sess. 378 (1994) (statement of Alexander W. Spears, Vice Chairman and Chief Operating Officer, Lorillard Tobacco Company); ATC letter to the Honorable Henry A. Waxman, note 355, *supra,* at pp. 2-3 of attachment. The evidence in this section demonstrates that nicotine levels in some cigarettes have not fallen proportionately with tar and, in fact, are subjected to independent manipulation and control.

[480] *See* 1979 *World Tobacco* article, note 426, *supra,* at page 95.

The manipulation of nicotine levels relative to tar levels in European cigarettes was noted in *The Lancet* in 1979. The author reported that the tar-to-nicotine ratio had declined from 1973 to 1979 and concluded that "the consistent fall in tar yield relative to nicotine over a period of years suggests an element of conscious manipulation." Tar: nicotine ratio of cigarettes 1973-79. *The Lancet.* No. 8139. August 25, 1979. Pages 422-423. [Emphasis added.]

[481] *See:*
Jacob P, Benowitz NL, Shulgin AT. Recent studies of nicotine metabolism in humans. *Pharmacology, Biochemistry, and Behavior.* 1988. Volume 30. Pages 249-250. In a more recent study, Benowitz states that cigarettes currently contain 8 to 9 mg of nicotine. Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction. *N Engl J Med.* 1994;331:123-125.

regardless of the labeled and advertised FTC nicotine yields and manufacturers' claims of low-nicotine delivery for certain brands, all cigarettes contained at least about 10 mg of nicotine in the cigarette rod. Consistent with this finding, a study by Benowitz and Hall et al.[482] in 1983 demonstrated that cigarettes advertised as having a low-nicotine yield do not contain less nicotine than high-yield cigarettes. Moreover, the nicotine yield of cigarettes, as defined by the FTC smoking machine tests, correlates inversely with nicotine concentrations in the tobacco.[483] In other words, cigarettes advertised as low-tar and low-nicotine have higher concentrations of nicotine, by weight, than high-yield cigarettes. This has been accomplished by a combination of the methods described above for boosting nicotine delivery to compensate for nicotine losses from the application of tar-reducing design modifications.

FDA's analysis of marketed cigarettes has disclosed similar results. There is little variation in nicotine content from one U.S. brand to another. FDA also measured the actual amount of nicotine contained in several brands of cigarettes, and the amount of nicotine in three varieties of the Merit brand of cigarettes: one regular, one low-tar, and one ultra low-tar. The results of this testing showed that the variety labeled and advertised as the lowest in nicotine actually had the highest nicotine concentration, suggesting that the nicotine content was

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Benowitz NL. Dosimetric studies of compensatory cigarette smoking. In: Wald N, Froggatt P, eds. *Nicotine, Smoking and The Low Tar Programme.* Oxford, England: Oxford University Press; 1989:chap 10.

[482] Benowitz NL, Hall SM, Herning RI, Jacob III P, Jones RT, Osman A. Smokers of low yield cigarettes do not consume less nicotine. *New England Journal of Medicine.* 1983;309:139-142.

[483] *Id.*

manipulated to compensate for reductions caused by design features intended to reduce tar.[484]

In addition, FDA evaluated the tar and nicotine data for domestically marketed cigarettes published by the FTC for 1994. These data demonstrate that the lowest tar products have a markedly higher ratio of nicotine to tar than higher tar products. None of the 153 products with 14 or more milligrams of tar (high tar) had a nicotine to tar ratio greater than 1 to 12. By contrast, 88 of the 93 products with 6 or fewer milligrams of tar (ultra-low tar) had a nicotine to tar ratio greater than 1 to 12.[485]

The increase in nicotine-to-tar ratios between 1972 and 1994, see note 485, especially in low tar cigarettes, is particularly revealing in the light of industry research dating from the 1970's showing that the "optimum" nicotine-to-tar ratio for acceptability of low tar cigarettes is higher than the "natural" ratio. As described earlier, a 1975 Philip Morris study showed that "the optimum nicotine-to-tar (N/T) ratio for a 10mg [low] tar cigarette is somewhat higher than

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[484] According to FDA's analysis, whereas Merit Regular 100's contained 1.46% nicotine, Merit Low Tar 100's contained 1.67% nicotine, and Merit Ultra Low Tar 100's contained 1.99% nicotine. *See Regulation of Tobacco Products (Part I): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representarives,* 103 Cong. 2d Sess. 121 (March 25, 1994) (statement of David A. Kessler, M.D., Commissioner of Food and Drugs, "The Control and Manipulation of Nicotine in Cigarettes," Chart P). The Commissioner's statement is included as Appendix 7 to this document.

[485] Federal Trade Commission. 1994 report of the tar and nicotine content of domestic cigarettes. (FDA's analysis included only those products that were evaluated by the Tobacco Industry Testing Laboratory.) By contrast, only 2 of the 142 marketed cigarettes included in the FTC report for 1972 had a nicotine to tar ratio greater than 1 to 12. (Federal Trade Commission. 1972 report of the tar and nicotine content of domestic cigarettes.) On a percentage basis, only 1.4 percent of the 1972 products had a nicotine to tar ratio greater than 1 to 12. In 1994, that figure grew to 26.3 percent overall, and rose to 95 percent for the 93 products in the lowest tar category. This suggests that as the market for lower yield cigarettes has grown over the last 20 years, the cigarette industry has altered the traditional ratio of nicotine to tar.

occurring in smoke from the natural state of tobacco."[485a] [Emphasis added.] The Philip Morris researchers went on to say that this study would be used to "attempt to make a 10 mg [low tar] cigarette that will equal a Marlboro in subjective acceptability and strength." According to these researchers, the naturally occurring nicotine-to-tar ratio was 0.07, while the optimal ratio was about 0.1. See p. 223, supra.[485b]

As noted above, tobacco industry officials have repeatedly stated that nicotine yields are not manipulated and are simply a function of tar yields, i.e., that reductions in tar yields result in proportionate reductions in nicotine yields. For example, the chief operating officer of Lorillard

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[485a] Low Delivery Cigarettes and Increased Nicotine/Tar Ratios, A Replication. Approved by W.L. Dunn and distributed to H. Wakeham. October, 1975. *In* 141 Cong. Rec. H8009 (daily ed. July 31, 1995)(statement of Rep. Waxman). *Also in* Hilts PJ. Documents Disclose Philip Morris Studied Nicotine's Effect on Body. *New York Times.* June 8, 1995.

[485b] According to an analysis of FTC nicotine and tar delivery levels conducted by a member of Congress, at least two Philip Morris low-tar products show evidence that the data on "optimal" nicotine-to tar ratios was applied by the company to make changes in the nicotine-to-tar ratios of marketed cigarettes. One marketed cigarette underwent an increase in its nicotine-to-tar ratio, beginning in 1978, that closely corresponds to the change from the "natural" ratio to the "optimum" ratio described by Philip Morris researchers in 1975. From 1968 to 1978, tar and nicotine levels in regular Benson & Hedges filtered cigarettes dropped from 21 mg tar and 1.29 mg nicotine to 0.9 mg tar and 0.06 mg nicotine. Throughout this period, the nicotine-to tar ratio in the cigarettes remained stable, i.e., tar and nicotine delivery levels were falling proportionately. The ratio during this period was 0.7, the ratio described by Philip Morris researchers as "natural" for tobacco. Then, beginning in 1978, nicotine delivery from Benson & Hedges began to increase, while tar remained stable. By 1983, the nicotine delivery had jumped from 0.06 to 0.1, an increase of over 60%. The result was an increase in the nicotine-to tar ratio to 0.11, approximately the same level found by Philip Morris researchers to be "optimal." Congressman Waxman reported that the chance that this change in the nicotine-to-tar ratio could have been due to random fluctuations in tar and nicotine levels is less than 1 in 100,000. The tar-to-nicotine ratio for Benson & Hedges dropped back to 0.07 in 1984 and 1985. Although the reasons for this change are unknown, Congressman Waxman noted that the change could have been due to a decision to phase out the product or to the use of technologies that permit manipulation of the amount of nicotine delivered to the smoker but that do not affect the amount of nicotine measured by a smoke machine. Waxman also analyzed Philip Morris product, Merit Ultra Lights. This product was introduced in 1981 with a nicotine/tar ratio of 0.11, which corresponds to the "optimal" ratio found by Philip Morris researchers, rather than to the "natural" ratio of 0.07. The elevated nicotine-to-tar ratio in Merit Ultra Lights has remained constant in the years since its introduction. 141 Cong. Rec. H8009-10 (daily ed. July 31, 1995)(statement of Rep. Waxman). Philip Morris denied that the changes were deliberate. Hilts PJ. Philip Morris Denies Charge By Lawmaker. *New York Times.* August 2, 1995.

Tobacco Co. testified before Congress in 1994 that:

> *We do not set nicotine levels for particular brands of cigarettes. Nicotine levels follow the tar level . . . . The correlation coefficient of 0.975 is essentially perfect correlation between tar and nicotine and shows that there is no manipulation of nicotine.*[485c]

The significant increase in the nicotine to tar ratio for low delivery products contradicts these statements and provides strong evidence that nicotine deliveries are independently manipulated. In fact, an industry document states that the nicotine-to-tar ratios in ultra low tar cigarettes are higher than would be expected if nicotine fell proportionately with tar. In 1978, Philip Morris surveyed the nicotine-to-tar ratios in its competitors' ultra low tar products (5-7 mg tar) and found that these ultra low tar cigarettes "seem to be higher in nicotine delivery than we would otherwise expect" and found further that "nicotine/tar ratios go up as tar goes down":

> *The table [of nicotine-to-tar ratios for a range of low tar brands] suggests that Philip Morris brands (asterisked) have lower nicotine/tar ratios than do other brands with about the same FTC tar delivery . . . . The table also suggests that nicotine/tar ratios go up as tar goes down, and that our competitors' brands . . . seem to be higher in nicotine delivery than we would otherwise expect from our own experience with low delivery cigarettes . . . .*
>
> *It appears therefore that the mechanics of cigarette engineering and the deliberate decisions of our competitors are such as to suggest high nicotine/tar ratios be used at ultra low tar levels.*[485d] [Emphasis added.]

The Philip Morris researchers suggest that the high nicotine-to-tar ratios in the low tar products of Philip Morris' competitors have been achieved through certain kinds of filters and by "the use of

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[485c] *Regulation of Tobacco Products (Part I): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives,* 103rd Cong., 2d Sess. 378 (1994) (statement of Alexander W. Spears, Vice Chairman and Chief Operating Officer, Lorillard Tobacco Company)

[485d] Memorandum to T.S. Osdene from W.L. Dunn. Plans and Objectives-1979. December 6, 1978. *In* 141 Cong. Rec. H7670 (daily ed. July 25, 1995).

high alkaloid blends,"[485e] i.e., the use of tobaccos containing high nicotine levels.

FDA also analyzed other information supplied by the FTC that was derived from the FTC's database on nicotine levels in cigarettes. FDA's analysis of the FTC data demonstrates two very important results. First, there is an apparent increase in the sales-weighted FTC nicotine delivery ratings, for all cigarettes, since 1982 (the earliest year for which the computer database is available). Second, consistent with the data on the increase in nicotine to tar ratios, when FDA segmented FTC's sales data into high-tar, low-tar, and ultra low-tar cigarettes, nicotine yields had the greatest increase in the ultra low-tar group.[486] These findings are depicted in the following charts:

[485e] *Id.*

[486] *See:*

Kessler, note 484, *supra,* at charts Q, R, S, T. "Sales-weighted" nicotine delivery ratings represent the average nicotine yield of all cigarette brands sold in a given year, adjusted (weighted) to reflect the actual sales of the brands.

Hoffman D, Hoffman I. On the Reduction in Cigarette Smoke. In: Wald and Froggatt, note 481, *supra,* at pp. 200-201.

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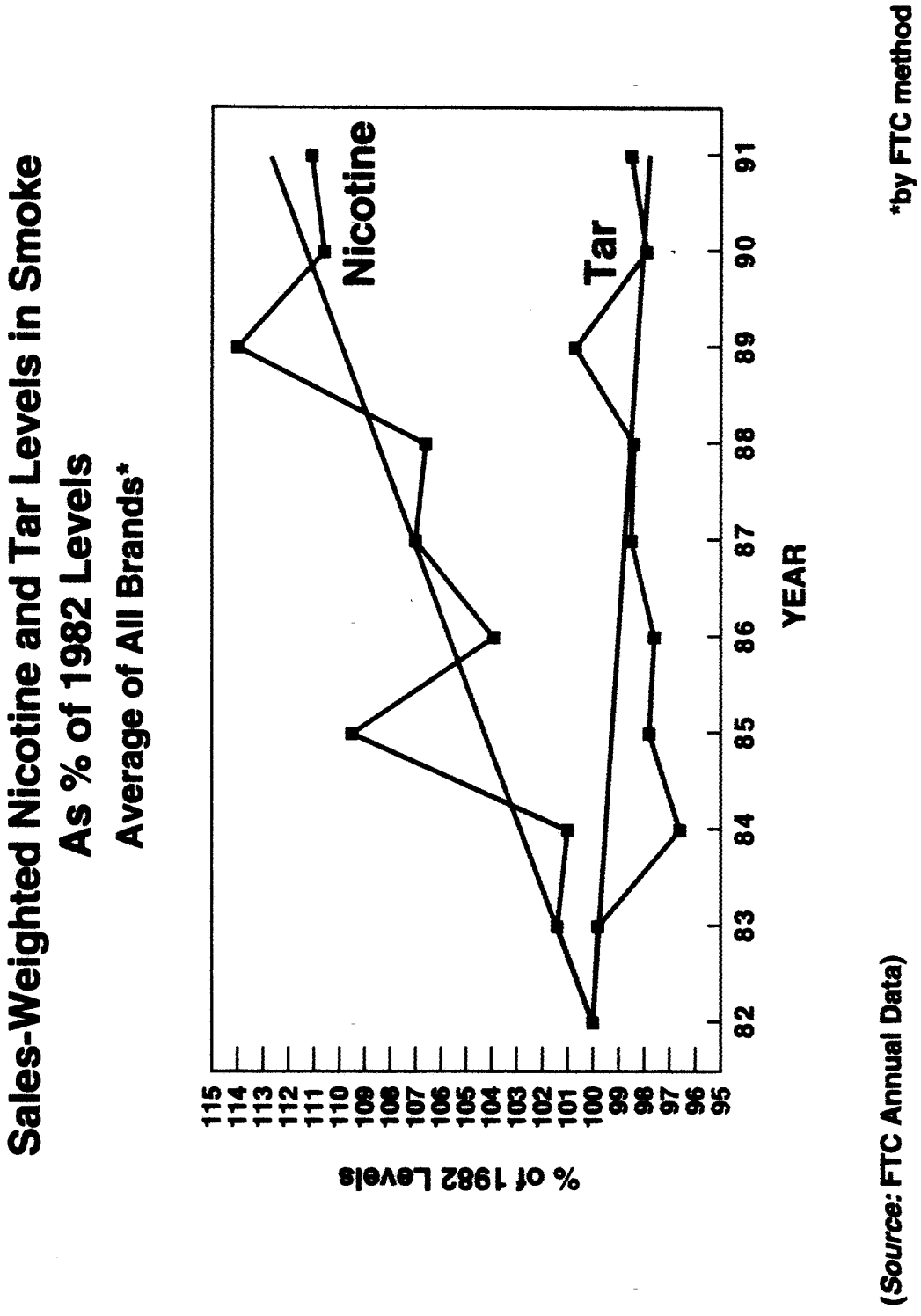

(*Source:* FTC Annual Data)

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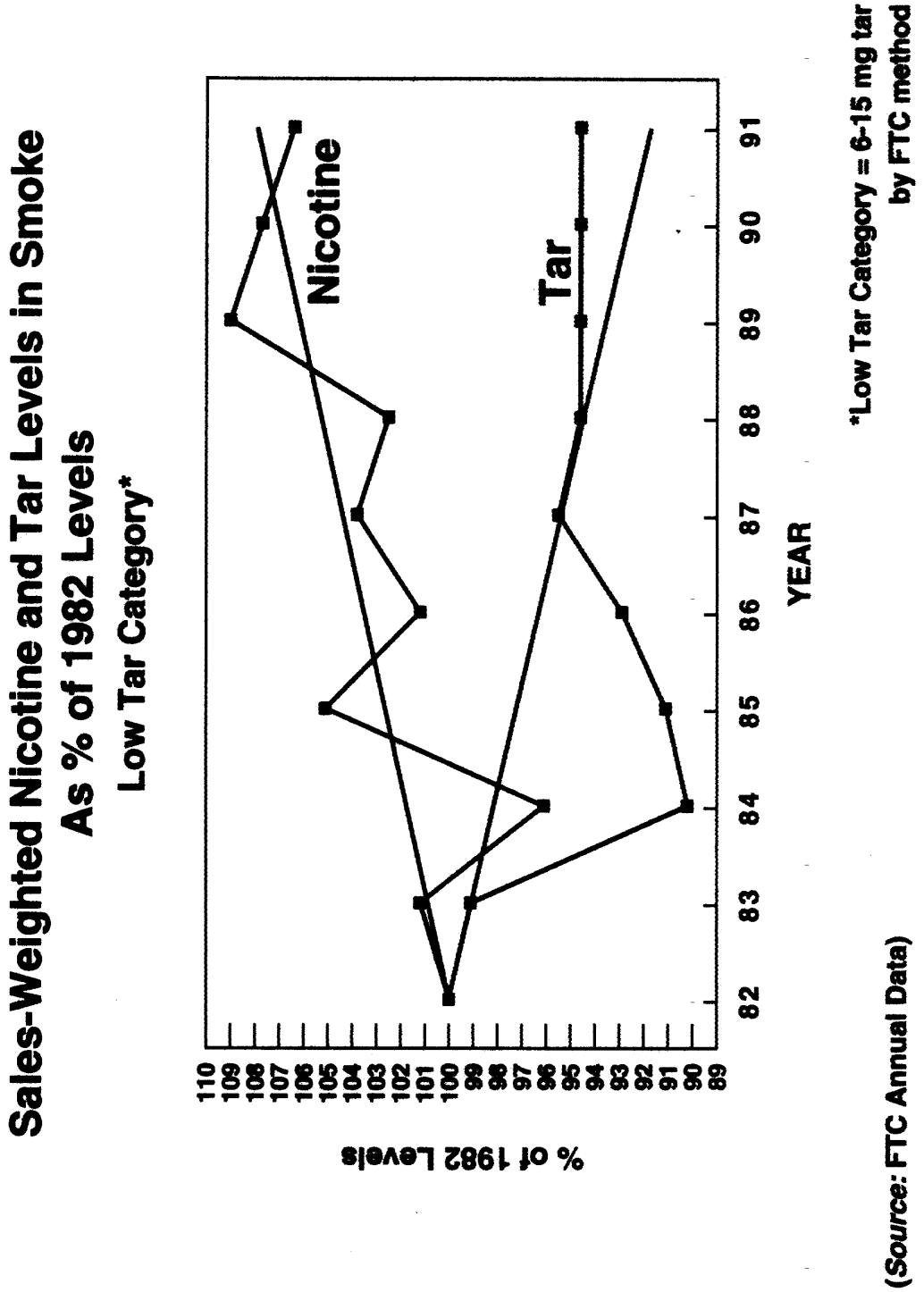
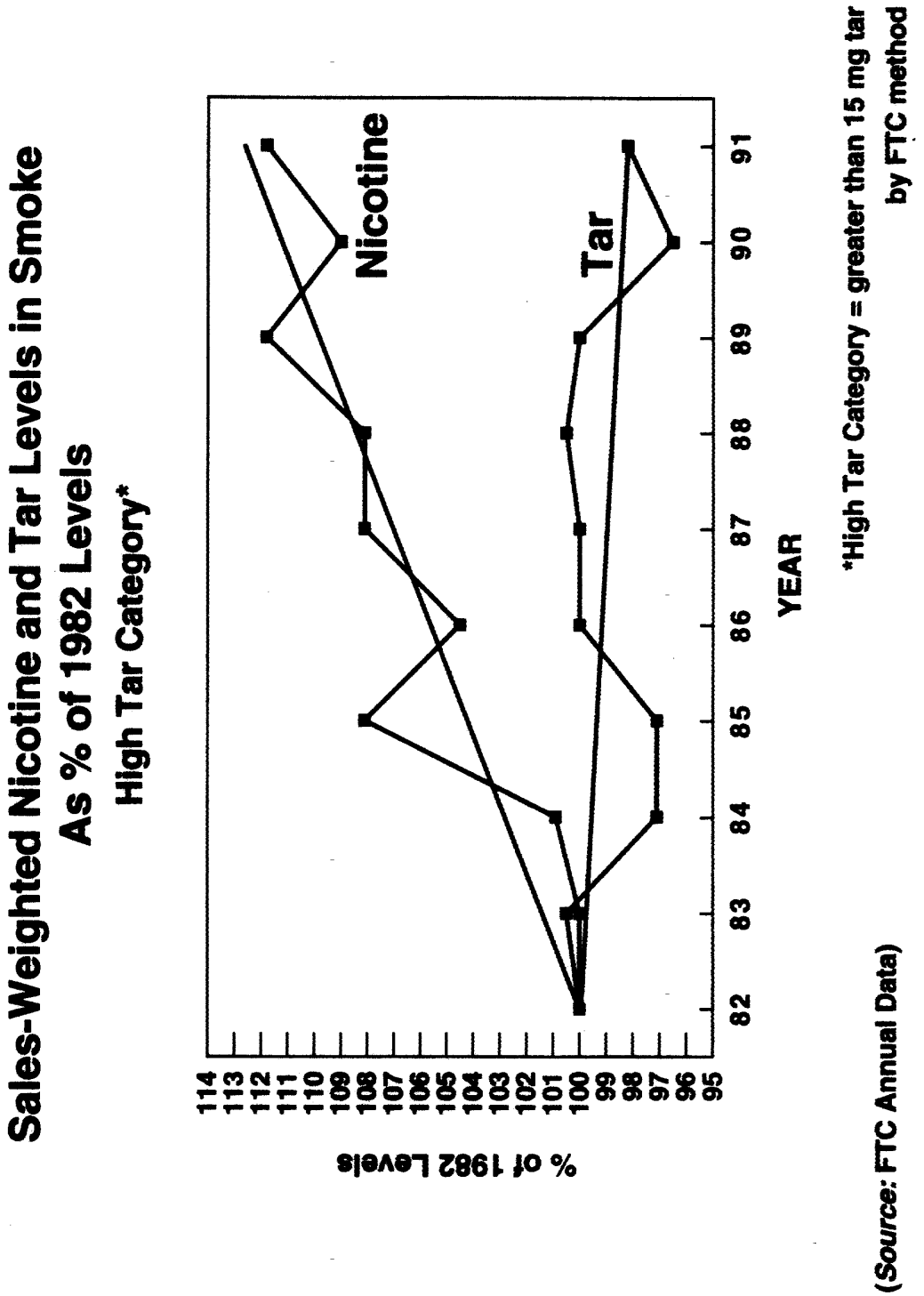

Sales-Weighted Nicotine and Tar Levels in Smoke
As % of 1982 Levels
Low Tar Category*
Nicotine
Tar
% of 1982 Levels
YEAR
110 109 108 107 106 105 104 103 102 101 100 99 98 97 96 95 94 93 92 91 90 89
82 83 84 85 86 87 88 89 90 91
*Low Tar Category = 6-15 mg tar by FTC method
(Source: FTC Annual Data)

269


Sales-Weighted Nicotine and Tar Levels in Smoke
As % of 1982 Levels
High Tar Category*
Nicotine
Tar
% of 1982 Levels
YEAR
82
83
84
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87
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91
95
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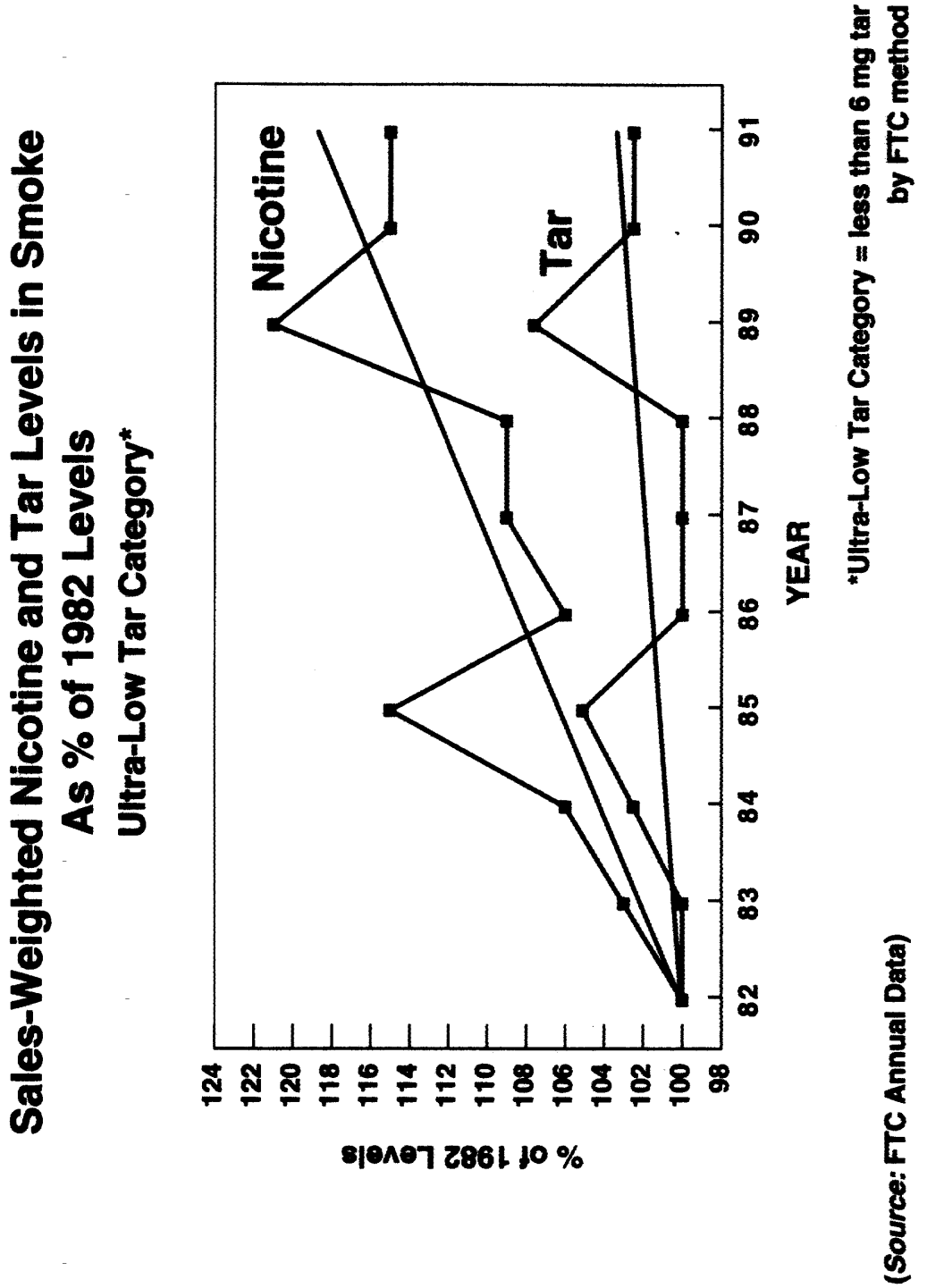
*High Tar Category = greater than 15 mg tar by FTC method
(Source: FTC Annual Data)

270


Sales-Weighted Nicotine and Tar Levels in Smoke
As % of 1982 Levels
Ultra-Low Tar Category*
Nicotine
Tar
% of 1982 Levels
124
122
120
118
116
114
112
110
108
106
104
102
100
98
82
83
84
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89
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91
YEAR
*Ultra-Low Tar Category = less than 6 mg tar by FTC method
(Source: FTC Annual Data)

f. Conclusion

The information in the preceding sections demonstrates that cigarette manufacturers manipulate and control the delivery of nicotine in marketed products. Cigarettes are designed to supply nicotine at consistent levels despite the wide variations in the nicotine levels of the raw materials, the immensely complicated combustion chemistry, and the complex chemical flow properties of a modern cigarette.

Manufacturers use many techniques to control nicotine deliveries. The application of these modifications in cigarette design and their interactive nature pose complex problems in maintaining brand uniformity and consistency regarding nicotine delivery. Yet, the nicotine content and delivery of each brand of cigarettes is remarkably consistent from batch-to-batch and year-to-year. This level of control is analogous to that of the pharmaceutical industry in the production of prescription drugs. In fact, to determine how well nicotine content is controlled in cigarettes, FDA laboratories compared the content uniformity of drugs in tablet or capsule form to the content uniformity of nicotine in cigarettes. The results showed that nicotine content varies from cigarette to cigarette no more than the content of active ingredients in marketed pharmaceuticals.[487]

FDA's investigation has also disclosed that the tobacco industry uses a number of methods to boost nicotine delivery in low-yield cigarettes. The cigarette industry has successfully used these methods to maintain adequate nicotine delivery from low-yield products. Without the independent manipulation of nicotine, many of the techniques used to reduce tar

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[487] FDA, CDER, DDA, Report on Analysis of Packages of Cigarettes, April 4, 1994. *See* Kessler, note 416, *supra*, at p. 12.

would also substantially reduce nicotine. Instead, regardless of differences in labeled/advertised FTC nicotine yields and manufacturers' claims of low-nicotine delivery for certain brands, all cigarettes contain approximately the same amount of nicotine in the rod, and deliver about 1 mg of nicotine, enough to produce pharmacological effects. See p. 108, supra. Moreover, studies by FDA and others have demonstrated that the lowest-yield cigarettes have the highest concentrations of nicotine, demonstrating that nicotine delivery has been independently manipulated.

The tobacco industry's control and manipulation of nicotine delivery from cigarettes provides additional evidence of the industry's intent to deliver pharmacologically satisfying levels of nicotine to smokers.

2. Industry Manipulation and Control of Nicotine in Smokeless Tobacco

Smokeless tobacco manufacturers control the delivery of nicotine from smokeless tobacco to produce a line of smokeless products that deliver nicotine in graduated amounts. Products that deliver lower doses of nicotine are marketed to new users of smokeless tobacco. Smokeless tobacco marketing then encourages them to "graduate" to products that deliver higher doses of nicotine. Smokeless tobacco manufacturers' manipulation of nicotine deliveries and marketing of low-nicotine products to new users and high-delivery nicotine products to experienced users demonstrates their intention to market products that facilitate nicotine dependence, a significant effect on the structure and function of the body. Smokeless tobacco manufacturers' products are thus intended to affect the structure and function of the body.

Moist snuff is the most popular form of smokeless tobacco. U.S. Tobacco Co. ("UST"), which accounts for 85% of the moist snuff sales in the U.S.[488] markets a line of moist snuff products that includes Skoal Bandits, Skoal Long Cut, Original Fine Cut Skoal, and Copenhagen. Skoal Bandits deliver a very small amount of absorbable nicotine, Skoal Long Cut and Original Fine Cut Skoal deliver sequentially more absorbable nicotine, while Copenhagen delivers the highest amount of absorbable nicotine. UST representatives in fact acknowledge that the company's products provide users with a range of nicotine deliveries.[489]

Smokeless tobacco manufacturers produce graduated nicotine delivery products primarily

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[488] *See* Appendix 5.

[489] *Marsee v. U.S. Tobacco,* note 317, *supra.* (Remarks of Mr. Finnegan, attorney for U.S. Tobacco.) In: 1.7 TPLR 3.202.

See also deposition of Erik Lindqvist, Senior Vice President for Marketing, U.S. Tobacco, in *Marsee v. U.S. Tobacco.* Transcript of Jury Trial Proceedings, at pp. 1648-1676.

by manipulating the pH of the tobacco.[490] Smokeless manufacturers add compounds and manipulate the design of each smokeless product to create a specific pH. The higher the pH of a product, the more nicotine is transformed from the salt form to "free nicotine." Both forms of nicotine are highly soluble in saliva. However, the free form of nicotine is absorbed more rapidly in the mouth of smokeless tobacco users and into the bloodstream for delivery to the brain. Raising the salivary pH from 7.0 to 8.0 increases the percentage of free nicotine available for absorption from 10% to 50%, a fivefold increase.[491]

Various documents show that UST understands the relationship between the pH of its products and their nicotine delivery. For example, in a deposition, UST's Senior Vice President for Marketing acknowledged that he had written a memo in which he had recommended a specific pH level for a new product and that he understood that there was a relationship between pH and nicotine.[492] When asked whether pH affected nicotine absorption, he agreed:

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[490] *See:*

Henningfield JE, Radzius A, Cone EJ. Estimation of available nicotine content of six smokeless tobacco products. (Submitted to *Tobacco Control* November 17, 1994.)

U.S. Food and Drug Administration. *Report on study of smokeless tobacco products: pH and free base nicotine.* November 4, 1994.

U.S. Food and Drug Administration. National Forensic Chemistry Center. Cincinnati Laboratory. *National survey of smokeless tobacco products.* December 13, 1994, memo from Laura Ciolino, Research Chemist to Fred Fricke, Director.

[491] *See:*

Armitage AK. Some recent observations relating to the absorption of nicotine from tobacco smoke. In: Dunn WL. ed. *Smoking Behavior: Motives and Incentives.* Washington, DC: VH Winston & Sons; 1973. Pages 86 (figure 2) and 87.

Henningfield JE, Radzius AC, Cooper TM, Clayton RR. Drinking coffee and carbonated beverages blocks absorption of nicotine from nicotine polacrilex gum. *JAMA.* 1990;264(12):1560.

[492] Transcript of Jury Trial Proceedings, *Marsee v. U.S. Tobacco*, note 317, *supra,* at pp. 1666-8.

Q. Mr Lindqvist, is it your understanding that as the pH of the product is lowered, that the rate of absorption of nicotine by the user is also lowered?

A. That would be my understanding, yes.[493]

The major smokeless tobacco manufacturers in the United States each market products that range from low to high pH, producing a corresponding graduation in the amount of "free nicotine" delivered by these products. The products with the lowest pH deliver the least amount of absorbable nicotine, while those with the highest pH deliver a significantly higher amount of absorbable nicotine.[494]

FDA laboratories comprehensively analyzed several marketed snuff products.[495] The following table demonstrates the characteristics of marketed smokeless tobacco products related to nicotine delivery.[496]

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[493] *Id.* at p. 1668.
See also:
U.S. Tobacco Company documents discuss the pH of various brands, also suggesting a knowledge of the relationship between pH and nicotine absorption:
Red Seal Menthol. . . 2. Lower pH than Skoal through flavor if possible. . . Premium project. . . Full tobacco flavor, pH at the level of Copenhagen or higher.
U.S. Tobacco memo from Erik Lindqvist. (This document was discussed in the trial in *Marsee v. U.S. Tobacco*, note 317, *supra*. These quotes were authenticated by Erik Lindqvist, the author, in his deposition. Transcript of Jury Trial Proceedings, at pp.1666-1671.)

According to the trial transcript of *Marsee*, UST recognizes that pH can affect how much of the nicotine is free. (U.S. Tobacco document No. 4486792, dated Oct. 5, 1981. In: 1.7 TPLR 3.208, July/August 1986.)

[494] The amount of absorbable nicotine is dependent on the pH and not the total amount of nicotine that is in the product. For this reason, the total amount of nicotine in the products throughout the product line can remain relatively constant and still permit graduated nicotine delivery.

[495] FDA laboratories in St. Louis and Cincinnati performed these studies. The results are summarized in two separate reports. *See* note 490, *supra*.

[496] This table reflects the two separate studies which were performed by the two FDA laboratories in St. Louis, MO and Cincinnati, OH. Both laboratories used the same analytical procedures for these analyses.

MANUFACTURER/ PRODUCT NAME	pH		% Free Nicotine*		Total Nicotine Content (mg/gm)**	
	St. Louis	Cinc.	St. Louis	Cinc.	St. Louis	Cinc.
U.S. Tobacco Co.						
Skoal Key	--	8.22	--	61.3	--	12.4
Copenhagen Snuff	8.14	7.71	56.5	32.7	13.2	13.8
Skoal L.C. Class.	8.04	7.92	51.1	45.5	12.7	13.8
Skoal L.C. Wint.	7.50	7.57	23.1	26.0	12.7	13.9
Skoal L.C. Mint.	7.35	7.52	17.6	24.0	13.2	13.7
Skoal L.C. Spear	7.20	7.50	14.0	23.3	12.5	13.8
Skoal Or.F.C. Wint.	--	7.41	--	19.7	--	13.6
Skoal L.C. Strai.	7.47	7.41	22.0	19.5	12.1	13.8
Skoal L.C. Cherry	7.15	7.38	12.3	18.5	12.5	13.6
Skoal Band. Mint	6.83	7.06	6.4	9.9	6.7	8.8
Skoal Band Wint.	6.56	6.72	3.3	4.8	7.8	8.2
Happy Days L.C. Mint	--	6.00	--	0.9	--	13.9
Skoal Band. Strai.	--	5.48	--	0.3	--	10.8
Skoal Band. Class.	5.61	5.23	0.39	0.2	10.4	9.9
Helme Tobacco Co.						
Redwood Full Flavor	--	7.52	--	24.0	--	12.6
Silver Cr. L.C.	--	7.22	--	13.7	--	6.0
Cooper Wint. L.C.	--	6.99	--	8.5	--	5.7
Gold River L.C.	--	5.77	--	0.6	--	6.4
C.C. Conwood Co.						
Kodiak Wint.	8.20	8.22	59.9	61.0	11.4	11.7
Kodiak Choice Wint.	--	7.98	--	47.7	--	11.4
Kodiak Straight	7.39	7.82	19.0	38.4	10.6	10.4
Hawken Wint.	5.56	5.58	0.35	0.4	4.4	4.0
Pinkerton Tobacco Co.						
Redman F.C. Ex. Wint.	--	7.58	--	12.3	--	--
Renegade Wint.	6.81	7.17	5.8	13.2	11.8	--

L.C. = long cut

* Calculated using the Henderson-Hasselbach equation for acid-base equilibrium. This calculation strictly is dependent on the pH determination. Any error in the pH determination will affect the percent free nicotine calculation.

** Measured on wet basis.

This table demonstrates that each of the smokeless tobacco companies whose products were tested by the FDA laboratories markets products that have low, medium, and high pH values, delivering corresponding low, medium, and high levels of free nicotine to the users of the products.[497] It is apparent from the data that providing graduated nicotine deliveries through manipulation of pH is an industry-wide practice. Other researchers have described similar findings.[498]

Other features of these products demonstrate how the smokeless tobacco companies use product design features to control nicotine delivery. For example, UST's Skoal Bandits and Pinkerton's Renegades are packaged in teabag-like pouches, which both limits the amount of snuff that is placed into the mouth and creates a barrier that retards nicotine release from the product. FDA laboratory analysis shows that the effect of the Bandits' pouch is to delay nicotine release by an average factor of three, compared to the same tobacco tested outside of the pouch, during the first 2 minutes of the study.[499] Thus, users of Skoal Bandits get less nicotine into their mouth, and the nicotine is released into their mouths at a slower rate.

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[497] In the chart, the first column lists the products marketed by specific manufacturers. For each manufacturer, the products are listed in descending order of nicotine delivery. The second and third columns list the pH of each product as measured by two separate FDA labs. The fourth and fifth columns list the amount of absorbable (free) nicotine in each product, calculated from the pH measured at each of the two labs. The sixth and seventh columns list the total nicotine content of each of the products as measured by each of the two labs.

[498] *See* Henningfield, note 490, *supra,* at p. 2. This study found that Skoal Bandits have a pH of about 6.9, providing only 7% of its nicotine in the free form. Skoal Long Cuts have a pH of about 7.4-7.5, providing 19%-23% free nicotine. Original Fine Cut Skoal has a pH of about 7.6, providing 28% free nicotine. Copenhagen was found to be a potent form of snuff, with a pH of about 8.6, producing 79% free nicotine, a very high level for absorption. Page 2 and figure 1.

[499] Department of Health and Human Services, FDA, National Forensic Chemistry Center. *Relative Buffering Capacity of Saliva and Moist Snuff* and *Moist Snuff Nicotine Content Code Date Survey.* Memorandum from Laura A. Ciolino to Elizabeth Berbakos and Thomas Layloff. September 28, 1994.

Smokeless tobacco products are also engineered in such a way that users get a bolus dose of nicotine within the first 5 minutes of inserting the product into the mouth.[500] After the first 5 minutes, nicotine is still released from the product but at a much slower rate. An FDA study showed widely divergent results when comparing Copenhagen and Skoal Bandits under typical use conditions.[501] The amount of nicotine released from a usual "pinch" of Copenhagen (about 1.5 gm) was 12 times higher than from a pouch of Bandits (about 0.5 grams) in the first 2 minutes of the experiment. The bolus dose results in nicotine concentrations in the bloodstream that produce a peak pharmacological concentration in users. These pharmacological concentrations are then maintained by the slow continued release of nicotine from the products following the bolus dose.

Both nicotine release and pH of smokeless products are also affected by the tobacco fermentation process used to make smokeless tobacco products. Tobacco fermentation causes an increase in pH with fermentation time.[502] The age of packaged smokeless products is thus a factor in each product's pH because fermentation can continue within the package due to the high

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[500] *See:*

U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Analysis. *Nicotine Studies of Chewing and Smokeless Tobacco Products.* Memorandum from Henry D. Drew, Chief, Drug Monitoring Branch, to Elizabeth Berbakos. September 22, 1994. Table 4.

U.S. Food and Drug Administration. National Forensic Chemistry Center. Cincinnati Laboratory. *Moist Snuff Nicotine Release Studies.* September 28, 1994, memo from Laura Ciolino, Research Chemist to Fred Fricke, Director. Page 1.

[501] *Id.* September 28, 1994, memorandum.

[502] Tso TC. *Kirk-Othmer Encyclopedia of Chemical Technology.* John Wiley and Sons; 1970;20:510. This occurs because organic acids are lost through oxidation and decarboxylation.

moisture content of the tobacco.[503] Because fermentation increases pH, and increasing pH increases free nicotine, continued fermentation increases the amount of nicotine that is delivered to smokeless tobacco users. Fermentation also breaks down the plant tissue. This results in nicotine release from the plant intracellular tissue, causing much of the nicotine to come to the surface of the tobacco leaf.[504]

Manufacturers also add humectants to their products to increase or maintain the moisture content. The resulting high moisture content of smokeless products affects nicotine delivery by ensuring that tobacco leaves are well wetted, thus allowing nicotine easily to go into solution (i.e., saliva).

The evidence demonstrates that smokeless tobacco manufacturers design their products to deliver controlled amounts of nicotine to the user by manipulating pH, placing starter products in pouches, and using additives that control the moisture content of the products. Smokeless manufacturers use these sophisticated design features to manipulate the pharmacological response of the user to the product. In doing so, manufacturers intend to market products that affect the structure or function of the body.

The marketing practices of the smokeless tobacco industry further demonstrate the intent of manufacturers to factilitate nicotine dependence among smokeless tobacco users. Until the 1970's, smokeless tobacco companies were marketing only products with high nicotine delivery.

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[503] Andersen RA, Fleming PD, Hamilton-Kemp TR, Hildebrand DF. pH changes in smokeless tobaccos undergoing nitrosation during prolonged storage: effects of moisture, temperature, and duration. *J. Agric. Food. Chem.* 1993;41:968-972.

[504] This may explain the fast nicotine release from the tobacco products studied by FDA under *in vitro* conditions.

Their market was steadily diminishing because these products were not well tolerated by new users. Evidence from the files of smokeless tobacco companies shows that, in the late 1960's or early 1970's, these companies began to try to entice new users of smokeless tobacco, including people as young as 15 years old.[505] To do so, they developed low-nicotine products in teabag-like pouches to encourage people to begin using smokeless tobacco. A UST document describes the company's rationale for developing a new oral snuff product under the code name "The Lotus Project":

AIM: *To make it easier for a new user to use tobacco in the mouth.*

TARGET GROUP: *New users, mainly cigarette smokers age group 15-35*

PRODUCT: *A. Strength*

1. Nicotine Satisfaction

Mild like Happy Days [a low-nicotine product]
Instant but not shocking

2. Feeling in the mouth

As little harshness as possible on the gum and in the throat

* * *

PACK: *A. Size of Pinch*

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[505] *See* documents on "Lotus Project":
Undated document entitled "The Lotus Project." From *Marsee v. U.S. Tobacco*, note 317, *supra*, Trial Exhibit 159.

U.S. Tobacco Co. Intra-company Correspondence from W.W. Watson, President - United Scandia International to Mr. L.A. Bantle, President. June 2, 1972. From *Marsee v. U.S. Tobacco*, Trial exhibit 158.

Minutes from a Meeting in Greenwich at Mr. L.A. Bantle's Office. July 18, 1972. From *Marsee v. U.S. Tobacco*, Trial exhibit 159.

> ***Small enough for a new user to manage . . . This point has to be closely worked out, takes into consideration the desired effect mentioned under "Strength."***[506]

This document clearly discloses UST's intention to develop a low-nicotine product suitable for "new users," i.e., those not yet tolerant to the harsh effects of nicotine on the gum and throat, and not yet requiring high levels of nicotine for "satisfaction."

Another UST document that discusses the "Lotus Project" and product development discloses the company's intent to produce products with varying amounts of nicotine.[507] The document states:

> *"[t]here should be three products of three different tastes and strengths of nicotine . . .*
>
> *a. High nicotine, strong tobacco flavor . . .*
>
> *b. Medium strength of nicotine. . .*
>
> *c. Low nicotine, sweet product. . ."*[508]

By acknowledging that the objective is to produce products with varying strengths of nicotine and differentiating strength from taste, the document demonstrates the company's intent to manufacture products with distinct pharmacological effects based on the nicotine delivery.

A document that posed potential questions and answers related to UST's introduction of Skoal Bandits in a new market also demonstrates the manufacturer's intention to provide nicotine

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[506] *Id.* Trial Exhibit 159 (minutes from July 18, 1972, meeting).

[507] *See* Watson, note 505, *supra,* at p. 2.

[508] *Id.*

for absorption and thereby to produce "satisfaction" in the user of the product.[509] The document provides the following questions and anwers about Skoal:

> *3. - How does it work ?*
>
> > *It gives the satisfaction from tobacco want* [sic]. *It is real tobacco and contains nicotine. . .*
>
> *4. - How much nicotine does it contain ? Is it absorbed ?*
>
> > *The nicotine contents are more or less equivalent to that of a good quality cigarette of average strength. The nicotine is absorbed, given [sic] satisfaction to the smoker.*

A senior UST official stated in another memorandum that "satisfaction" refers to the "kick" that users obtain from tobacco products.[510]

Shortly after the "Lotus Project" documents were written, UST began to aggressively market the low-nicotine "starter" products to new users of smokeless tobacco. An early advertisement for "Happy Days," one of the first low-nicotine products, targeted the product "for you guys just starting out."[511] The marketing of starter products relied heavily on "sampling," a technique in which company representatives distribute free samples on college campuses and sports events, and encourage nonusers to use smokeless tobacco.[512] Advertisements then

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[509] *Potential Questions and Answers.* Bate stamp nos. 2054948-2054951, submitted in *Marsee v. U.S. Tobacco*, note 317, *supra.*

[510] *Marsee v. U.S. Tobacco*, note 317, *supra.* Deposition of Erik Lindqvist, Senior Vice President, Marketing. Transcript of Jury Trial Proceedings, at p.1662.

[511] Connelly GN. In the search for a perfect starter product: manipulation of nicotine in oral snuff brands. August 1994. (Unpublished.)

[512] U.S. Tobacco Company. College Representative Manual. Revised July 31, 1985:
Success in reaching the college students today will determine the continued popularity and growth for our products in our adult market segments tomorrow.

Achieving these goals will require strong consumer sampling efforts. Success in this area can

encouraged established users to graduate to higher-nicotine products. For example, an advertisement for Copenhagen, the highest nicotine product, said "Sooner or Later, It's Copenhagen."[513]

In the 1980's, "long cut" smokeless tobacco products were introduced. An internal UST memorandum, dated June 8, 1984, reported that customers and distributors of the Skoal "Long Cut" considered it a "'perfect' starter product," in part due to its relatively low "strength" (i.e., low delivery of nicotine).[514] This memorandum also acknowledges the role of low-nicotine products in facilitating graduation to high-nicotine brands like Copenhagen. In a long list of positive anecdotes about the introduction of Long Cut, the memorandum states that college representatives reported that "Long Cut makes it easier to become accustomed to using Cope[enhagen]" as well as "having sampled a person with Long Cut, and then seeing that person weeks later as a regular Cope consumer."[515] The same memorandum reports that Copenhagen sales "continue to rise on a weekly basis since the intro of Long Cut."[516]

A chart prepared by UST's marketing department further demonstrates the company's knowledge that consumer use of its products follows the graduated nicotine deliveries of those products and shows the company's desire to capitalize on a "graduation process" to enhance sales

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only be achieved with an aggressive, efficient program. . .

[513] Connelly, note 511, *supra*, at p. 5.

[514] U.S. Tobacco Company. Intra-company Correspondence from K.C. Carlsen to O.M. Bryant. *Skoal Long Cut.* June 8, 1984. Page 1.

[515] *Id.* at pp. 2-3.

[516] *Id.* at p. 2.

of its highest nicotine products.[517] The chart is labeled "graduation process" and shows a hierarchy of products, with arrows pointing from Skoal Bandits to Happy Days and Skoal Long Cuts, and culminating with Copenhagen. This "graduation" corresponds exactly to the progression of nicotine deliveries from the listed products.

The company's reliance on the graduation process is further evidenced in a UST document entitled "Expanding User Base", which depicts a "bullseye" chart that lists the company's moist snuff products.[518] The chart follows:

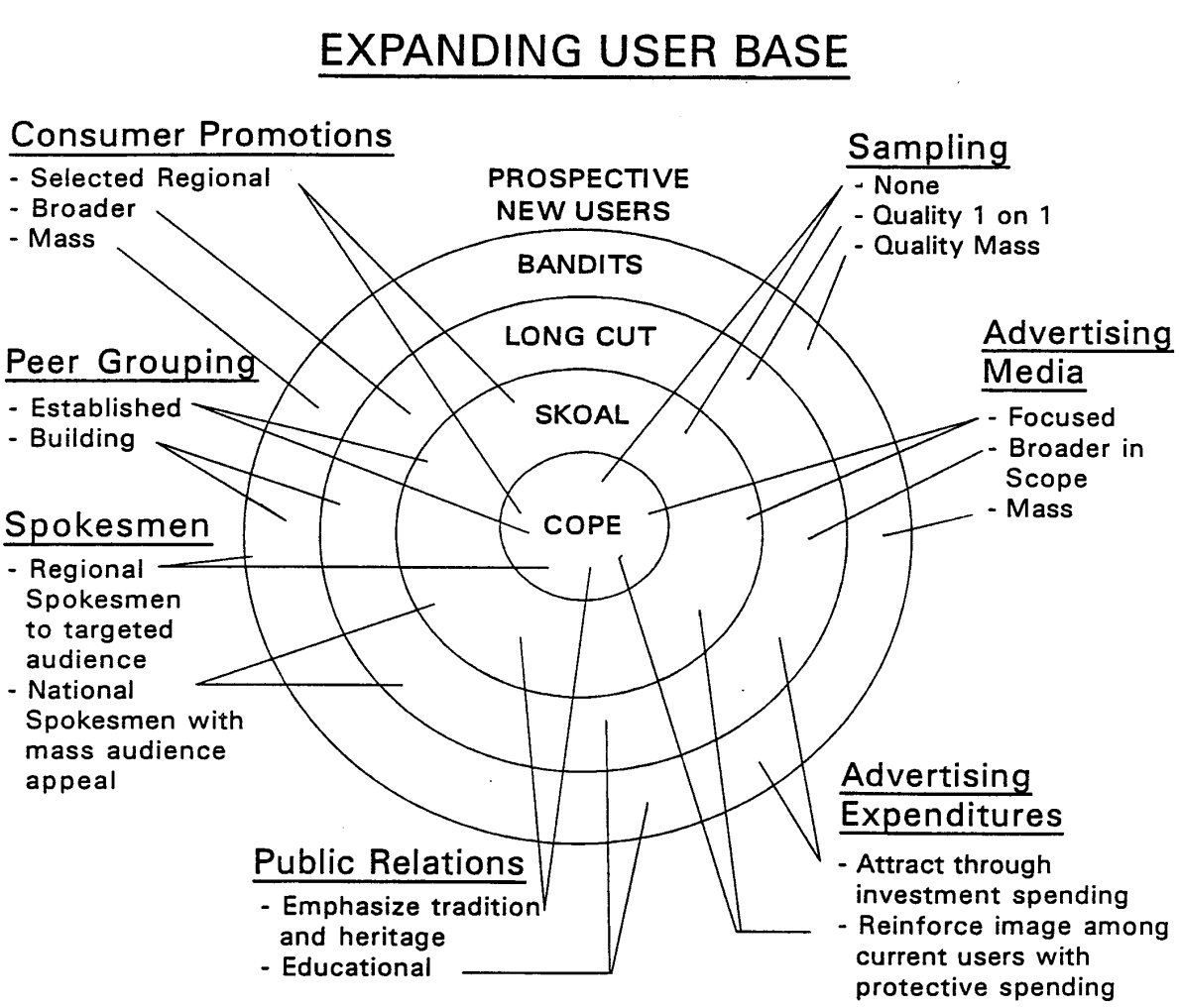
[517] *Marsee v. U.S. Tobacco*, note 317, *supra*, Plaintiff's Exhibit 100, "Graduation Process." (Undated.)

See also U.S. Tobacco Company. One-on-one interview with Mr. Manuel Leitao, Executive Vice President, U.S. Tobacco and President Tobacco Division. *Up to Snuff.* Autumn 1984:2:

> *Some people will remain with the Bandits, and some people will get into a sort of graduation process. The bottom line, and we must never forget the bottom line, is that Bandits is a vehicle that is going to expand the use of smokeless tobacco.*

Another company document sets out a similar strategy for entering new markets. The strategy involved starting users on the lower nicotine Skoal Bandits with an eye toward "establishing a normal graduation process." U.S. Tobacco Company. International Division-Very Optimistic About U.S. Tobacco's Worldwide Expansion. *Up to Snuff.* March 15, 1988. Page 2.

[518] U.S. Tobacco Company. *Expanding User Base.* (Undated.) This document was disclosed during discovery in *Marsee v. U.S. Tobacco,* note 317, *supra.* The document was authenticated by Dr. Jack Henningfield in a letter to Rep. Henry Waxman (D-Ca), in which Dr. Henningfield states his awareness of the origins of the chart as "provided by the United States Tobacco Company to the plaintiffs in the *Marsee v. United States Tobacco Company* law suit in which I served as an expert witness in 1986. This chart was provided to me by the plaintiffs attorney, Mr. Braly, to review." Letter from Jack E. Henningfield, Ph.D., Chief, Clinical Pharmacology Branch, National Institute on Drug Abuse to The Honorable Henry A. Waxman, Chairman, Subcommittee on Health and the Environment, House of Representatives (Dec. 13, 1994).



Adapted from a chart provided by U.S. Tobacco during discovery in Marsee v. U.S. Tobacco

Outside the outermost ring of the chart is the label "Prospective New Users"; the subsequent concentric rings are labeled "Bandits," "Long Cut, and "Skoal," respectively, and a ring labeled "Cope" (representing Copenhagen) is the bullseye in the middle. The rings of the chart thus progress from the lowest delivery nicotine products on the outside to the highest nicotine delivery products in the center of the bullseye. The chart's further annotations - - "Consumer Promotions," "Peer Grouping," "Spokesmen," "Public Relations," "Advertising Expenditures," "Advertising Media," and "Sampling" - - clearly demonstrate the company's intent to advertise, promote, and provide free samples of the lower delivery nicotine products, which are on the lowest level of the "graduation process," to new users. The highest nicotine products, however, are to be advertised only to current users in a highly focused manner.

Several other company documents discuss the graduation process. A UST document discussed in a trial transcript mentions Skoal Bandits and the company's intent to use the product to fuel the graduation process:

> *Skoal Bandits, which is at the bottom of the previous graduation chart, 'will continue to fuel the new user base to assure graduation to our priority moist brands'.*[519]

Another UST document, discussed in the same trial transcript, again acknowledges the company's deliberate use of the graduation process:

> *. . . sample Skoal Bandits often and intensively in and around the retail account to create new customers and feed the graduation process.*[520]

These marketing strategies for smokeless tobacco have been extremely successful in

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[519] UST document No. 2077832, in *Marsee v. U.S. Tobacco,* note 317, *supra.* In:1.7 TPLR 3.209. Another U.S. Tobacco document (no. 1023186-89), discussed in *Marsee* mentions introducing a product that will fill the gap between Bandits and Skoal in the graduation process. In:1.7 TPLR 3.209.

[520] UST document No. 2101576, discussed in *Marsee v. U.S. Tobacco*, note 317, *supra* (1.7 TPLR 3.210).

recruiting new users. Use of smokeless tobacco products has risen substantially since the 1970's: overall, consumption of moist snuff almost tripled from 1972 through 1991; use by adolescent males aged 18 to 19 increased almost 1,500% between 1970 and 1991.[521] The success of the graduation strategy in getting users to the point where they want to consume the high-nicotine products is demonstrated by the market share of various products. While the majority of advertising dollars are spent on the low and medium nicotine products like Skoal Long Cuts, the great bulk of the increased sales is in Copenhagen, the high-nicotine product.[522] The consistently small market share for the low-nicotine products shows that they serve only as a steppingstone to the high-nicotine products. Consistent with the graduation strategy, a recent study found that older smokeless tobacco users are more likely to purchase the brands that deliver high levels of nicotine than are younger smokeless tobacco users.[523]

The evidence of manipulation of nicotine delivery in smokeless tobacco and the deliberate marketing of higher and higher nicotine-containing products shows clearly that smokeless tobacco manufacturers intend consumers to become tolerant to, and dependent on, the

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[521] *See:*

Centers for Disease Control and Prevention. Office of Smoking and Health. Unpublished data from 1970 and 1991 National Household Interview Surveys. (Rate of snuff use among 18-19 year-old males was 0.5% in 1970 and 7.6% in 1991).

Marcus AC, Crane LA, Shopland DR, Lynn WR. Use of smokeless tobacco in the United States: Recent estimates from the current population survey. In: *Smokeless Tobacco Use in the United States: NCI Monographs.* 1989;8:17-23.

Sullivan LW. Keynote Address. In: *Smokeless Tobacco or Health: An International Perspective: Smoking and Tobacco Control Monograph 2.* National Cancer Institute. NIH Pub. No. 92-3461. 1992.

[522] *See* Connolly, note 511, *supra,* at p. 5.

[523] Hatsukami D, Nelson R, Jensen J. Smokeless tobacco: current status and future directions. *Brit. J. of Addiction.* 1991; 86:559-563.

nicotine in smokeless tobacco. Both tolerance and dependence are effects on the structure and function of the body produced by nicotine. Accordingly, smokeless tobacco products, as designed and marketed by the tobacco industry, are intended to affect the structure or function of the body.

F. INDUSTRY ALTERNATIVE TOBACCO PRODUCTS

1. Industry Development of Nicotine Substitutes That Mimic Nicotine's Drug Effects

Tobacco manufacturers' intention to offer tobacco products that will be used to affect the structure or function of the body is further demonstrated by the research programs tobacco companies have undertaken to develop "nicotine analogues." Nicotine analogues are chemical substances that are closely related to nicotine. Both Philip Morris and Brown and Williamson have had substantial research programs to identify nicotine analogues that would produce nicotine-like effects on the central nervous system[524] and that either could be substituted for nicotine if nicotine-containing tobacco became regulated or unattractive to consumers, or that could be added to currently marketed products to enhance the effects of nicotine.

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[524] *See the following documents:*

Kilburn KD, Underwood JG. BATCO Group Research and Development Center. *Preparation and Properties of Nicotine Analogues*. Report No. RD 953-R. November 9, 1972.

Kilburn KD, Underwood JG. BATCO Group Research and Development Center. *Preparation and Properties of Nicotine Analogues, Part II.* Report No. RD 1048-R. October 11, 1973

Kilburn KD. BATCO Group Research and Development Center. *Preparation and Properties of Nicotine Analogues, Part III.* June 20, 1979.

BATCO R&D. *Notes on the R&D Conference*. October 29, 1979 - November 1, 1979. Page 01794-01808.

Declaration of former Philip Morris scientist Victor John DeNoble, Ph.D., executed on February 2, 1995. (hereafter cited as DeNoble Declaration) (A copy of the declaration is on file at FDA.)

The Council for Tobacco Research - U.S.A. and the American Tobacco Co. also funded research on nicotine analogues. *See, e.g.:*

Report of the Council for Tobacco Research - U.S.A., Inc. 1978.

Meacham RH, Bowman ER, McKennis H. Additional routes in the metabolism of nicotine to 3 pyridylacetate. The metabolism of dihydrometanicotine. *J-Biol-Chem.* 1972;247(3):902-08.

These programs were also designed to identify substances that shared nicotine's "desired" effects on the central nervous system, without producing nicotine's undesirable effects on the cardiovascular system.[525] In the words of former Philip Morris scientist Dr. Victor J. DeNoble:

> *Our goal was to identify the effects of nicotine in the central nervous system, and to establish structural activity relationships among organically synthesized analogues of nicotine. The purpose of this nicotine analogue program was to develop an analogue that would retain the physiological effects of nicotine in the brain as well as the behavioral effects, but not have adverse effects on the cardiovascular system.*[526]

The tobacco industry's programs to develop nicotine analogues were, according to company documents, prompted by the industry's recognition that the market for tobacco depends on the pharmacological effects of nicotine on the central nervous system. For example, in 1968, BATCO researchers reported the following conclusion at a research conference:

> *In view of its pre-eminent importance, the pharmacology of nicotine should continue to be kept under review and attention paid to the possible discovery of other substances possessing the desired features of brain stimulation and stress-relief without direct effects on the circulatory system. The possibility that nicotine and other substances together may exert effects larger than either separately (synergism) should be studied and if necessary the attention of Marketing Departments should be drawn to these possibilities.* [Emphasis

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[525] BATCO R&D. BATCO Research Conference. Hilton Head, SC. September 24-30, 1968. Page 3.

See also:
U.S. Patent No. 5,138,062. Osdene TS, Secor HV, Seeman JI. *Nicotine Analogues*. Philip Morris Inc. August 11, 1992. C1:57-60.

U.S. Patent No. 5,015,741. Osdene TS, Secor HV, Seeman JI. *Nicotine Analogues*. Philip Morris Inc. May 14, 1991. C1:56-60.

See DeNoble Declaration, note 524, *supra,* at pp. 3-4.

[526] *Regulation of Tobacco Products (Part 2): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce. U.S. House of Representatives.* 103rd Cong. 2d Sess. 5 (April 28, 1994) (testimony of former Philip Morris scientist Victor J. DeNoble).

added.][527]

This document shows that BATCO was interested in using chemicals with nicotine-like effects to replace nicotine or enhance the drug effects of nicotine in cigarettes.[528] Another BATCO document underscores the fact that the search for nicotine analogues was designed to implement the industry's belief that nicotine's drug effects are essential to sustain the market for tobacco. S.J. Green, director of research at BATCO, in a paper on future research policy, stated:

> *While other factors cannot be ignored and their influence is not completely understood, it seems a good assumption that nicotine plays a predominant role for many smokers. So that a good part of the tobacco industry is concerned with the administration of nicotine to consumers. If this assumption is correct two long-range research projects become immediately apparent. These are to find pharmacological alternatives to nicotine and to explore alternatives to tobacco as a source of nicotine.*[529]

Other documents show that nicotine analogues were also believed by BATCO to be necessary to protect against three potential threats to the company's nicotine-based market: 1) government action to prohibit the use of nicotine because of nicotine's cardiovascular toxicity; 2) the development by other pharmaceutical companies of alternative, more socially and medically acceptable means of administering nicotine; or 3) the discovery and use by pharmaceutical companies or anti-tobacco activists of nicotine "antagonists," that is, substances that block the

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[527] *See* BATCO Research Conference, note 525, *supra,* at p. 3.

[528] *See also* U.S. Patent No. 4,340,072. Bolt AJ, Chard B. *Smokable Device.* Imperial Group Ltd. (1982). This patent describes an alternative cigarette-like device providing an aerosol that may contain nicotine or another psychoactive substance:

> *The aerosol material may, as an alternative to a flavourant solution, comprise a solution of a flavourant and/or nicotine in triacetin or benzyl benzoate. Any psycho-active or physiologically active compound such as ephedrine or a nicotine/ephedrine mixture may be used.*

[529] Green SJ. *BAT Group Research.* September 4, 1968. Page 2.

effects of nicotine on the central nervous system.

A BATCO research report dated November 9, 1972, and entitled "Preparation and Properties of Nicotine Analogues," provided the following rationale for BATCO's long-term research program to develop nicotine analogues:

> *Summary*
> *Should nicotine become less attractive to smokers, the future of the tobacco industry would become less secure.*
>
> *Factors that could influence the attractiveness of nicotine are discussed, and it is concluded that substances closely related to nicotine in structure (nicotine analogues) could be important.*
>
> . . . .
>
> *Introduction*
> *It has been suggested that a considerable proportion of smokers depend on the pharmacological action of nicotine for their motivation to continue smoking (1, 2, 3[530]).*
>
> *If this view is correct, the present scale of the tobacco industry is largely dependent on the intensity and nature of the pharmacological action of nicotine.*
>
> *A commercial threat would arise if either an alternative product became acceptable or the effect of nicotine was changed.*
>
> *An alternative product could come from the pharmaceutical industry. With a socially acceptable route for administration, and with medical endorsement, the product could be successful.*
>
> *The effect of nicotine could be inhibited by an antagonist, and cigarettes would tend to become insipid. Such an antagonist could arise by accident or design from the pharmaceutical industry. It might be used tactically to advance that industry's alternative product, or its general use could be advocated by the anti-smoking lobby, with or without government support.*
>
> *The obvious starting point of a search, either for alternatives or antagonists to nicotine, is the nicotine molecule and close analogues of it. The present report*

[530] The page of the report that contains the citations for these footnotes is missing from the document provided by Brown and Williamson to Congress.

discussed nicotine and some of its analogues. . .[531]

These internal documents reflect the tobacco industry's awareness that nicotine's drug effects are critical to the continued success of tobacco in the marketplace. Indeed, they show that the industry views nicotine's drug effects as so important that if nicotine's drug effects were interfered with in any way, tobacco companies would seek to substitute another drug for nicotine to ensure the continued market for tobacco.

Internal documents from Philip Morris' nicotine analogue program show that this company also sought nicotine analogues with pharmacological effects on the central nervous system, including effects associated with addiction.

For example, an internal 1980 company memorandum describes the rationale for Philip Morris' research into nicotine analogues. After asserting that nicotine "is a powerful pharmacological agent" which is "cited often as 'the reason for smoking,'" the memorandum describes the importance of discovering compounds related to nicotine:

> *[O]ur ability to ascertain the structural features of the nicotine molecule which are responsible for its various pharmacological properties can lead to the design of compounds with enhanced desirable properties (central nervous system effects) and minimized suspect properties (peripheral nervous system effects). There are many opportunities for acquiring proprietary compounds which can serve as a firm foundation for new and innovative products in the future.*[532]

Between 1980 and 1984, Dr. DeNoble conducted research for Philip Morris on nicotine analogues,[533] first identifying the pharmacological effects of nicotine on the brains and behavior

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[531] *See* Kilburn (1972), note 524, *supra,* at pp. 1-2.

[532] Philip Morris Interoffice Correspondence from J.L. Charles to Dr. R. B. Seligman. Nicotine Receptor Program-University of Rochester. March 18, 1980.

[533] The nicotine analogue program at Philip Morris began before Dr. DeNoble's arrival. *See*, e.g. Secor HV, Edwards WB. Philip Morris Research Center. Nicotine analogues: synthesis of pyridylazetidines. *J.*

of animals[534] and then comparing these effects to the physiological and pharmacological effects of nicotine analogues synthesized by chemists at Philip Morris.[535] Dr. DeNoble's studies, which were conducted as part of the "Behavioral Pharmacology" Program at Philip Morris, were intended to characterize the pharmacologic effects of nicotine and then to identify those analogues that affected the central nervous system in the same way that nicotine affects the central nervous system. An internal Philip Morris document states:

> *Major objectives of the Behavioral Pharmacology Program are (1) To develop a better understanding of the reinforcing actions of nicotine and nicotine*

Org. Chem. 1979;44(18):3136.

See DeNoble Declaration, note 524, *supra,* at p. 4.

[534] Dunn WL. Philip Morris Inter-Office Correspondence to T.S. Osdene. *Possible Restructuring of the Behavioral Research Lab.* June 18, 1980. Page 100019244.

[535] *See:*
DeNoble Declaration, note 524, *supra,* at pp. 2-9.

U.S. Patent No. 4,452,984. Edwards III WB. *Optically Active Nicotine Analogues and Process For Their Preparation.* Philip Morris Inc. June 5, 1984.

U.S. Patent No. 4,442,292. Edwards III WB. *Optically Active Nicotine Analogues and Process For Their Preparation.* Philip Morris Inc. April 10, 1984.

U.S. Patent No. 4,332,945. Edwards III WB. *Optically Active Nicotine Analogues and Process For Their Preparation.* Philip Morris Inc. June 1, 1982.

U.S. Patent No. 4,321,387. Chavdarian CG, Sanders EB. *Process for the Preparation of Optically Active Nicotine Analogues.* Philip Morris Inc. March 23, 1982.

U.S. Patent No. 4,220,781. Sanders EB, Secor HV, Seeman JI. *Process for Preparing 2-ALKYL Nicotinoids.* Philip Morris Inc. September 2, 1980.

U.S. Patent No. 4,155,909. Sanders EB, Secor HV, Seeman JI. *2-ALKYL Nicotinoids and Processes For Their Production.* Philip Morris Inc. May 22, 1979.

Work on nicotine analogues continued after Dr. DeNoble's departure from the company. *See* U.S. Patent No. 5,138,062, note 525, *supra.*; U.S. Patent No. 5,015,741, note 525, *supra.*; U.S. Patent No. 4,590,278. Edwards III WB. *Nicotine Analogues.* Philip Morris Inc. May 20, 1986.

analogues, (2) To gain insight into the neurobehavioral actions of nicotine, and (3) To develop and use animal behavior techniques to screen nicotine analogues for their nicotine eliciting properties.[536]

Dr. DeNoble's research and that of other scientists working at Philip Morris on the pharmacologic effects of nicotine showed that nicotine is self-administered by rats (i.e., is a "positive reinforcer"), produces tolerance, causes a unique "prostration syndrome" when injected into the rat brain that correlates to nicotine's ability to produce behavioral changes, and that nicotine loses its effects when the rat is pretreated with mecamylamine, a substance that blocks nicotine's effects in the brain.[537] These studies also demonstrated that nicotine has pharmacological activity in the brain, and that it has characteristics of other addictive substances that make it likely to be abused.[538] To evaluate potential nicotine analogues, Philip Morris tested numerous substances to determine whether they duplicated nicotine's effects on the brain and whether they had the same characteristics associated with abuse liability.[539] Dr. DeNoble and

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[536] DeNoble VJ, Carron L. Philip Morris Inter-Office Correspondence to Dr. T. Osdene. *Progress Report: The Behavioral Pharmacology Program.* October 14, 1980.

See Dunn, note 534, *supra,* which proposes the creation of the "Behavioral Pharmacology Project."

[537] *See:*
DeNoble Declaration, note 524, *supra,* at pp. 5-9.

DeNoble VJ. Philip Morris Inter-Office Correspondence to W.L. Dunn. *Nicotine Program-Behavioral Research Laboratory.* April 24, 1980. Page 2.

DeNoble VJ, Mele PC, Ryan FJ. Philip Morris Research Center. *Nicotine as a Positive Reinforcer for Rats: Effects of Infusion Dose and Fixed Ratio Size.* Unpublished Manuscript.

Dunn, note 534, *supra,* at p. 100019244.

[538] *See* DeNoble Declaration, note 524, *supra,* at pp. 7-9. *See also* FINDINGS § II.A.2., *supra.*

[539] *See:*
DeNoble, note 536, *supra.*

other scientists working at and for Philip Morris used nicotine analogues in discrimination tests in rats, in prostration studies, and in self-administration studies.[540] As noted in FINDINGS § I.B.3., supra, discrimination and self-administration studies provide key evidence of the likelihood that a substance will be addictive in humans.

Philip Morris documents state explicitly that the purpose of the research on nicotine analogues was to find nicotine substitutes that were behaviorally active and had the same reinforcing properties as nicotine; i.e., produced effects on the central nervous system associated with addiction. A progress report from the behavioral pharmacology group identified as its major objectives:

> *Nicotine Analogues*
>
> *Research Objectives*
>
> 1. *Determine if behaviorally active nicotine analogues can be directly substituted for nicotine in rats for which nicotine is functioning as an intravenously delivered positive reinforcer.*
> 2. *Establish nicotine analogues as an intravenously delivered positive reinforcer.*
> 3. *Compare the potencies of nicotine analogues to nicotine in producing positive reinforcing effects.*[541]

The objectives of the studies conducted by the behavioral pharmacology group were developed in conjunction with senior management at Philip Morris, and the study results were shared with

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DeNoble Declaration, note 524, *supra,* at pp. 4-5.

[540] DeNoble VJ, Carron L. Philip Morris Inter-Office Correspondence to W.L Dunn. *Research Progress Concerning Discrimination and Prostration Studies.* August 18, 1980. Pages 1003030001-1003030007.

Carron LM, Levy CJ, Allen A. Philip Morris Inter-Office Correspondence to V.J. DeNoble. *Discrimination Studies.* May 7, 1980. Pages 1003030008, 1003030009.

[541] DeNoble VJ, Carron L. Philip Morris Inter-Office Correspondence to W. Dunn. *Progress in Behavior Pharmacology Laboratory.* March 27, 1981. Pages 1-32.

upper management as well.[542]

Thus, it is evident from tobacco manufacturers' interest in developing nicotine analogues with central nervous system effects comparable to nicotine that these manufacturers (1) believe that the pharmacological effects of nicotine on the central nervous system, and in particular the pharmacological effects that reinforce continued tobacco use, are necessary to ensure a long-term market for tobacco; and (2) intend to market products that affect the central nervous systems of their customers.

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[542] *See:*
DeNoble Declaration, note 524, *supra,* at pp. 4, 11-12.

Charles JL. Philip Morris Inter-Office Correspondence to T.S. Osdene. March 1, 1983. Page 2: "Because of the sensitive nature of Vic's assignment, documentation of much of his work has been restricted to the Director and Vice President level."

2. Industry Research on Acetaldehyde As a Reinforcer

The behavioral pharmacology program at Philip Morris also conducted pharmacological and behavioral research on another constituent of cigarette smoke, acetaldehyde. This research was intended to find a combined dose of acetaldehyde and nicotine in cigarettes that would produce "maximal reinforcing effects."[543] The reinforcing capability of a drug is a measure of the dependence-producing properties of a drug.[544] In undertaking research on how to maximize the reinforcing effects of cigarettes, Philip Morris demonstrated its understanding of the dependence-producing nature of cigarettes and its intention to manufacture and sell cigarettes that affect the structure or function of the smoker's body.

Acetaldehyde, like nicotine, is present in, and delivered to the smoker from, cigarette smoke.[545] At the time Philip Morris conducted research on the reinforcing properties of acetaldehyde in cigarettes, acetaldehyde had been studied as a potential contributing factor to the

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[543] DeNoble VJ. Philip Morris U.S.A. Inter-office correspondence to J.L. Charles. *Project Number 1610 (Behavioral Pharmacology) Objectives and Plans - 1982-1983.* July 20, 1982. Page 2.

[544] *See:*

Balster RL. Drug abuse potential evaluation in animals. *Brit. J. of Addiction.* 1991;86:1549-1558.

Henningfield JE, Cohen C, Heishman SJ. Drug self-administration methods in abuse liability evaluation. *Brit. J. of Addiction.* 1991;86:1571-1577.

Griffiths RR, Lamb RJ, Ator NA, Roache JD, Brady JV. Relative abuse liability of triazolam: experimental assessment in animals and humans. *Neuroscience and Biobehavioral Reviews.* 1985;9:133-151.

[545] Acetaldehyde is present in tobacco at 1.6 - 7.4 mg/gm of processed tobacco. It is contained in mainstream smoke at 18-1400 mg per cigarette. U.S. Department of Health and Human Services. *Reducing the Health Consequences of Smoking: 25 Years of Progress. A Report of U.S. Surgeon General.* U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. DHHS Publication No. (CDC) 89-8411, 1989.

rewarding effects of alcohol.[546] This information led Philip Morris to explore its reinforcing properties in cigarettes.[547]

Researchers in Philip Morris' behavioral pharmacology program first conducted studies that showed that acetaldehyde acts on the brain and is a positive reinforcer when present in amounts comparable to those delivered by cigarette smoke.[548] By this time, the company had already demonstrated that nicotine was also a positive reinforcer. The researchers noted that it was well-known that the presence of two reinforcers together can modify the behavioral effect of either one, and decided to study whether rats would self-administer nicotine and acetaldehyde in combination. Recognizing that the reinforcing effects of nicotine and acetaldehyde are pharmacological, the researchers stated that their efforts were intended to determine whether the combination produced a "modification of the pharmacologic effect of one compound by the other."[549] The researchers found that rats self-administered the combination of acetaldehyde and

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[546] *See:*
Schuckit MA, Rayses V. Ethanol ingestion: Differences in blood acetaldehyde concentrations in relatives of alcoholics and controls. *Science.* 1979;203:54-55.

Brown ZW, Amit Z, Smith B. Intraventricular self-administration of acetaldehyde and voluntary consumption of ethanol in rats. *Behavioral and Neural Biology.* 1980;28:150-155.

[547] *See* DeNoble Declaration, note 524, *supra,* at p.10.

[548] *See:*
DeNoble VJ. Philip Morris U.S.A. Inter-office correspondence to W.L. Dunn. *Progress Report* from the Behavioral Pharmacology Laboratory for the period beginning September 1, 1980, to March 30, 1981. August 24, 1981. Pages 12-16.

DeNoble Declaration, note 524, *supra,* at pp. 10-11.

[549] DeNoble VJ, Mele PC. Philip Morris U.S.A. Inter-office correspondence to W.L. Dunn. *Progress Report* from the Behavioral Pharmacology Laboratory for the period beginning March 1, 1981, to March 1, 1982. April 21, 1982. Pages 18-19.

nicotine to a greater extent than either compound alone.[550] This finding suggested that the combination was a more potent positive reinforcer than nicotine or acetaldehyde alone.[551]

The culmination of this research was Philip Morris' attempt to establish the "optimum" ratio of acetaldehyde to nicotine in cigarette smoke:

> *Since both acetaldehyde and nicotine are reinforcing agents and each are contained in smoke it becomes important to determine [sic] ratio of acetaldehyde to nicotine which produce maximal reinforcing effects... This will allow us to determine the optimum ratio of acetaldehyde to nicotine that maintains the most behavior.*[552] [Emphasis added.]

As this passage makes clear, Philip Morris viewed the "optimal" ratio of acetaldehyde to nicotine as the ratio that would maximize the positive reinforcing effects of cigarettes; i.e., maximize their potential to produce dependence in smokers.

The behavioral pharmacology group conducted further studies suggesting that the ratio of acetaldehyde to nicotine that produced the greatest positive reinforcement in rats was in the range of 4:1.[553] While FDA does not know whether or how this research was implemented by Philip Morris, Dr. DeNoble was present at a meeting at which Philip Morris officials discussed the possibility of producing a cigarette with this ratio of acetaldehyde to nicotine and test-

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[550] *Id.* at pp. 19-21.

[551] *See* DeNoble Declaration, note 524, *supra,* at p. 11.

[552] DeNoble, note 543, *supra,* at p. 2.

[553] Philip Morris U.S.A. Behavioral Pharmacology Annual Report - June 1, 1983. Philip Morris Research Center. Richmond, VA. Pages 20-23. This work was still going on at the time the Behavioral Pharmacology program was terminated at the Philip Morris Research Center in Richmond, VA.

See also, DeNoble VJ. Philip Morris U.S.A. Inter-office correspondence to J.L. Charles. *Project 1610 (Behavioral Pharmacology) Objectives and Plans, 1984.* September 6, 1983. (Continued research on the ratio of acetaldehyde and nicotine with optimum reinforcing effects scheduled for 1984.)

marketing it in South America.[554]

It is thus clear that Philip Morris was interested in implementing the research to maximize the reinforcing effects of cigarettes by manipulating acetaldehyde and nicotine. The data on the reinforcing properties of particular ratios of acetaldehyde and nicotine were also used by researchers at Philip Morris to predict cigarette sales based on the delivery of nicotine and acetaldehyde. The researchers found that they could predict sales of particular brands with an accuracy above 80 % by comparing nicotine and acetaldehyde ratios.[555] This evidence compellingly demonstrates Philip Morris' reliance on, and intention to increase, the reinforcing effect of cigarettes on the structure or function of the smoker's body.

[554] *See* DeNoble Declaration, note 524, *supra,* at p. 12.

[555] *Id.* at p. 11.

3. Industry Development of Alternative Cigarettes That Deliver Nicotine

Tobacco companies have developed a number of cigarette alternatives. These alternatives to conventional cigarettes have generally been created in response to perceived societal pressure to market safer cigarettes. In developing cigarette alternatives, tobacco companies have sought to eliminate many of the traditional components and characteristics of cigarettes and cigarette smoke, such as tar and carbon monoxide. Tobacco companies have consistently recognized, however, that cigarette alternatives must deliver adequate amounts of nicotine to satisfy consumers. As a result, most of the alternative cigarette products developed by tobacco companies are simply nicotine delivery systems.

Tobacco company development of alternatives to cigarettes demonstrates the industry's knowledge that nicotine is the critical or "active" ingredient in cigarettes, and that smokers smoke primarily to obtain nicotine. The nature of the alternatives they believe could be substituted for currently marketed tobacco products strongly supports the inference that companies intend currently marketed tobacco products to serve as nicotine delivery systems.

In the late 1980's, RJR developed Premier, a "smokeless" cigarette that contained very little tobacco.[556] Although designed to be "smoked" and inhaled, Premier actually worked by

[556] Premier resembled a conventional cigarette in outward appearance only. It contained a carbon tip which served as the heat source. RJR informed FDA that at least 70% of the nicotine delivered by "Premier" was provided from spray-dried tobacco. This nicotine source had been combined with glycerol and adsorbed within alpha-alumina spheres contained within an aluminum cylinder positioned directly behind the carbon heat source. The remaining nicotine was provided from the cut tobacco leaf surrounding this cylinder and the tobacco extract-treated paper filter positioned in front of the cellulose acetate filter. Letter with enclosures from Peter B. Hutt, outside counsel for RJR, to Kevin M. Budich, FDA, January 26, 1988.

heating rather than burning tobacco.[557] RJR claimed that by altering the composition of conventional cigarettes and by eliminating the pyrolysis products produced by burning, Premier reduced by about 90% the chemical compounds delivered to smokers by conventional cigarettes.[558] Virtually the only compound (other than the paper and the filter) that was present in Premier in quantities similar to conventional cigarettes was nicotine.[559]

RJR's willingness to eliminate from Premier almost every conventional cigarette component but nicotine was not a coincidence. According to a memorandum of meeting dated October 23, 1987, the attorney representing RJR told FDA officials that for a cigarette substitute like Premier to be successful in the marketplace, it must contain nicotine.[560] Observing that herbal cigarettes had failed as substitutes due to the absence of nicotine, the attorney said that RJR would never eliminate nicotine from Premier because "without nicotine, you don't have a cigarette."[561]

RJR documents also show that the purpose of including nicotine in Premier was to deliver nicotine to the smoker's blood and brain. Studies conducted by RJR to determine

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[557] *See* R.J. Reynolds, note 300, *supra*. Premier was withdrawn from the market shortly after its introduction.

[558] *Id.* at p. 8.

Department of Health and Human Services. *RJR's "Smokeless" Cigarette*. October 23, 1987, memorandum of meeting between Peter B. Hutt, representing RJR Nabisco Inc., and FDA representatives (Daniel L. Michels, Sammie R. Young, Rudolf Apodaca, and Kevin M. Budich).

[559] *See* R.J. Reynolds, note 300, *supra,* at pp. 1-10. In the mainstream smoke produced by Premier, the only components that were similar in quantity to conventional cigarettes were nicotine and carbon dioxide.

[560] *See* Memorandum of Meeting, note 558, *supra.*

[561] *Id.*

whether Premier would be an acceptable cigarette substitute show unequivocally that RJR was interested in Premier's ability to deliver specific blood levels of nicotine to the smoker. Delivery of nicotine to the smoker's blood is relevant only if the company was interested in producing physiological effects in the smoker's body. The company itself reported, in a book published at the time of Premier's introduction, that it wanted to assess whether differences in composition and function between Premier and conventional cigarettes might alter nicotine delivery to the smoker's blood and body.[562] To assure itself that the absorption of nicotine into the smoker's body from Premier and conventional cigarettes was similar, RJR conducted plasma studies on rats and humans comparing the levels of nicotine in smokers' blood produced by smoking conventional cigarettes with the levels of nicotine produced by smoking Premier.[563]

RJR found the absorption and elimination of nicotine from Premier to be comparable to conventional cigarettes.[564] Because, however, Premier contained somewhat less nicotine than the reference cigarette tested, the blood levels of nicotine found in smokers of Premier were somewhat lower than those from the reference cigarette. The blood-level studies conducted by

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[562] *See* R.J. Reynolds, note 300, *supra,* at p. 460.

[563] During its investigation FDA asked R.J. Reynolds about the company's use of human body fluid testing to measure nicotine levels in smokers. Counsel to R.J. Reynolds informed FDA that it "should come as no surprise to the Agency that RJRT [R.J. Reynolds Tobacco Company] did some body fluids testing and used the services of Bellomy Research, Inc. to solicit participants." Letter to E. Blumberg, FDA, from R. Cooper, Williams & Connolly, on behalf of R. J. Reynolds. November 18, 1994. Page 2. It appears that R.J. Reynolds has conducted such testing not only in conjunction with the development of Premier, but in other circumstances "in which a developmental product incorporated new technology, and the testing was conducted in order to understand . . . for example, whether nicotine is absorbed or metabolized differently by smokers smoking the new technology product when compared to other cigarettes . . ." *Id.*

[564] *See* R.J. Reynolds, note 300, *supra,* at pp. 496-497. *See also* p. xii:
. . . in the short-term measurements of nicotine pharmacokinetics, the [Peer Review] Committee agreed with the conclusion that there was no significant difference in this response in individuals smoking either the reference or the new cigarette.

RJR demonstrated that smokers compensated for the lower levels of nicotine in Premier. The researchers stated that subjects smoked Premier more intensely, speculating that they inhaled a greater volume of the smoke from Premier.[565] Thus, while Premier contained about 52% of the nicotine of the reference cigarette, after 39 days of smoking Premier the volunteers were absorbing 69% of the nicotine they had absorbed from the reference cigarette.[566] RJR has patented other cigarette alternatives whose basic function is also to deliver nicotine.[567]

More recently, RJR detailed plans to unveil a low-smoke cigarette, Eclipse, in 1995. It has a charcoal heat source for the tip. Behind the charcoal tip, there are processed tobacco parts containing more than 50% glycerine, which vaporizes at temperatures below those that burn tobacco. Behind the processed tobacco, there is blended tobacco. The charcoal heats the processed tobacco and glycerine, which creates smoke-like vapor. The glycerine vapor then passes through the blended tobacco, picking up flavor and nicotine before passing through a standard cellulose filter, and into the smoker's mouth. According to RJR, Eclipse vapor contains about 85% water, glycerol, and nicotine (versus 25% in standard cigarette smoke) and about 15% tars and related particles (versus 75% in standard smoke).[568]

Other tobacco companies have also developed cigarette alternatives similar to Premier in design and intent. In the 1960's, Charles Ellis of BATCO developed "Ariel." Like Premier,

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[565] *Id.* at p. 482.

[566] *Id.* at pp. 479, 482-483, 490-492.

[567] U.S. Patent No. 5,285,798. Banerjee et al. *Tobacco smoking article with electrochemical heat source.* R.J. Reynolds Tobacco Company. February 15, 1994. (Alternative cigarette that is designed to generate enough heat, without burning, to volatilize and deliver to the smoker only the nicotine and flavor materials in the tobacco).

[568] Hilts P. Little smoke, little tar, but still lots of nicotine. *New York Times.* November 27, 1994;A1.

Ariel eliminated most of the compounds delivered by conventional cigarettes, but ensured delivery of a sufficient amount of nicotine to satisfy smokers' need for nicotine. Ariel was an alternative smoking device that contained a capsule of nicotine-enriched tobacco. The nicotine-enriched tobacco was heated by burning tobacco surrounding the capsule.[569] The nicotine was supposed to be released into an aerosol and inhaled by the smoker. The patents for this device make clear that its purpose was to provide an alternative to conventional cigarettes that would provide the same "satisfaction" as a traditional cigarette. The principal (indeed, almost the only) ingredient it was designed to deliver to achieve this goal was nicotine:

> *This invention relates to an improved smoking device whereby an improved smoke stream of a controlled character is delivered to the smoker.*
>
> . . . .
>
> *A further object is the provision of an improved smoking device of the above character which simulates a conventional or traditional smoking device, such as a cigarette, in appearance and in social habit attributes, and which affords the same benefits, pleasure and satisfaction without the attendant disadvantages.*
>
> . . . .
>
> *Our invention contemplates the provision of an improved smoking device having the appearance of a traditional smoking device and embodying a composition which releases nicotine vapor and potentially aerosol forming materials, including water vapor, when subjected to an elevated temperature . . .*[570]

A subsequent patent for a modification of this device stated that:

> *the invention thus seeks primarily to furnish a smoking device which will yield nicotine in an acceptable form, both psychologically and physiologically, but without the necessity for taking into the system so much of the products of combustion as is usual when*

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[569] *See:*

U.S. Patent No. 3,258,015. Ellis CD, Dean C, Schachner H, Williamson D. *Smoking Device*. Battelle Memorial Institute. June 28, 1966.

U.S. Patent No. 3,356,094. Ellis CD, Dean C, Hughes IW. *Smoking Devices*. Battelle Memorial Institute. December 5, 1967.

[570] *See* U.S. Patent No. 3,258,015, note 569, *supra*.

smoking a conventional cigarette . . .[571] [Emphasis added.]

At a 1968 conference of BATCO researchers, the conferees succinctly described Ariel as a "device[] for the controlled administration of nicotine."[572]

Other documents reveal that tobacco companies have consistently recognized that alternative tobacco products must contain sufficient amounts of nicotine to satisfy users.[573] For example, the minutes of a BATCO Group R&D Conference held in 1969 disclose that the conferees agreed that non-tobacco cigarettes could not succeed in the marketplace without the addition of nicotine:

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[571] *See* U.S. Patent No. 3,356,094, note 569, *supra.*

[572] BATCO Research Conference. Hilton Head Island, SC. September 24-30, 1968. Page 3.

[573] *See the following documents:*
BATCO Group Research Conference. St. Adele, Quebec. November 9-13, 1970.

S.J. Green. *Appendix I. Smoking and Health: Some Recent Findings.* Memo to D.S.F. Hobson. March 2, 1967. Page 2:
A non-tobacco smoking material has been made from cellulose and nicotine . . .

Proceedings of the BATCO Smoking Behaviour - Marketing Conference. July 9-12, 1984.

Ayres CI. *Notes from the 1984 GR&DC Nicotine Conference.* Conference Outline. July 9-12, 1984.

U. S. Patent No. 5,050,621. Creighton DE, Grieg CC. *Smoking Articles.* BATCO. September 24, 1991.
Abstract: There is provided a smoking article comprising a heating unit aerosol generation section in flow communication at a first end thereof with the heating unit, nicotine source in flow communication at a first end thereof with said heating unit, a mixing space with which said aerosol generation section and nicotine source means are in flow communication at or via respective second ends thereof, and a velocity accelerating orifice in flow communication with the mixing space. [Emphasis added.]

In a document submitted to the Food and Drug Administration in 1985 pursuant to an FDA examination of their product, Advance Tobacco Products, Inc., offered the following description of their smokeless cigarette:
[It] has the appearance and feel and provides a sensation similar to a conventional cigarette, but [ ] delivers nicotine satisfaction to the user by inhalation of nicotine vapor in a manner not requiring the combustion of tobacco.

> *There was a general discussion on non-tobacco materials and, largely due to the difficulties foreseen with the addition of nicotine, the Conference did not envisage at present the likely success of a totally non-tobacco cigarette.*[574]

The conferees went on to express their view that, if non-tobacco ingredients were used as part of the tobacco blend in cigarettes, cigarette manufacturers would have to compensate for the absence of nicotine in the non-tobacco materials by using high-nicotine tobaccos:

> *However, it now seems quite likely that non-tobacco materials will be successfully incorporated into cigarettes as blend constituents, particularly in health orientated products. A large usage of non-tobacco materials would be likely to increase the demand for high-nicotine tobaccos.*[575]

A 1970 BATCO R&D Conference included a particularly telling illustration of the tobacco industry's recognition of the central importance of nicotine in cigarette alternatives. The minutes of that conference contain the following finding, agreed to by the conference attendees:

> *It was agreed that, if and when total cigarette consumption declined, great opportunities for supplying the demands of other socially acceptable habits could follow. Discussion followed on those opportunities which might arise. Amongst those discussed were a) chewing products, and b) wet snuff* [both of which are smokeless tobacco products]. *It was felt that this whole area, much of which is already in the tobacco industry, should be examined more thoroughly. Particular attention should be given to buccal administration of nicotine and other physiologically active ingredients. At the same time, it was re-affirmed that we would not contemplate the incorporation of nicotine in edible products.*[576] [Emphasis added.]

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[574] BATCO Research Conference. Kronberg, Germany. June 6, 1969. Page 8. Brown and Williamson representatives attended.

[575] *Id.*

See also, BATCO, note 573, *supra,* at p. 4. A similar expression of the need to increase the nicotine content of the tobacco blend where tobacco substitutes without nicotine are used as part of the blend is contained in the minutes of a 1970 BATCO research conference:

> *The addition of nicotine to SM [a tobacco substitute] was considered, and it was recommended that nicotine per se, should not be used inside any tobacco factory. However, high nicotine content tobacco extract might be added.*

[576] *Id.* BATCO Group Research Conference at p. 3.

In 1984, BATCO marketers and "product application thinkers" convened to discuss innovative product ideas and were still convinced that if the tobacco industry lost a significant number of smokers, the industry should move to administration of nicotine through moist snuff. According to the conferees, the objective of shifting to moist snuff would be:

> *To capitalise on the potential downtrend of the smoking habit as the only means to achieve nicotine satisfaction by participating in a parallel product market free of social/health concerns and with attractive profitability.*[577] [Emphasis added.]

As these passages make clear, tobacco manufacturers understand that what both cigarettes and smokeless tobacco products have in common is the ability to administer nicotine to consumers, and that the purpose of the nicotine is to produce physiological effects on the consumer. If nicotine-containing cigarettes were to become socially unacceptable, it was the tobacco industry's intention to find another method of supplying nicotine to consumers.

Smokeless tobacco manufacturers, like cigarette manufacturers, understand that tobacco substitutes must include nicotine. Unlike BATCO, however, the major smokeless tobacco manufacturer, UST, has considered adding nicotine to food to create a nicotine delivery system that would function as an alternative to smokeless tobacco. At a meeting of UST executives, researchers, and marketers held in 1968 to discuss future directions for the company, the director of research proposed that the company develop a "swallowable chew: a confection with nicotine (artificial snuff)."[578] Later in the same document, he made clear that the purpose of adding nicotine to artificial snuff would be to "satisfy" snuff users;[579] i.e., to satisfy their need for

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[577] BATCO. *Structured Creativity Conference*. Southampton, England. June 25-28, 1984. List C.

[578] Minutes of Snuff and Chewing Tobacco Research - Manufacturing - Marketing Meeting. New York Hilton. January 22-23, 1968. Page 5.

[579] *Id.* at p. 10.

nicotine.

Thus, company documents related to the development of alternatives to cigarettes and smokeless tobacco establish tobacco manufacturers' knowledge that nicotine is the critical or "active" ingredient in cigarettes and smokeless tobacco, and that consumers use these products primarily for nicotine. Moreover, the fact that currently marketed and alternative products are studied for their ability to deliver nicotine to the bloodstream shows that the companies know that consumers use currently marketed tobacco products for the effects of nicotine on the structure and function of their bodies, rather than for taste or flavor. The fact that the tobacco industry considers nicotine delivery systems to be functional equivalents to tobacco demonstrates that tobacco companies intend their currently marketed tobacco products to deliver nicotine to consumers to affect the structure or function of their bodies.

G. INDUSTRY KNOWLEDGE THAT NICOTINE'S SENSORY EFFECTS ARE SECONDARY TO ITS PHARMACOLOGICAL EFFECTS

Despite the tobacco industry's public assertions that nicotine is in cigarettes only to provide flavor, taste, or mouth feel (immediate sensory effects) to the smoker,[580] the evidence shows that tobacco companies view nicotine's primary role as providing the smoker with the pharmacological effects that smokers seek from tobacco.

As described earlier, the tobacco industry knows that the primary significance of nicotine in tobacco is to provide pharmacological effects, both acute (mood regulation, weight control) and long-term (reinforcing effects that create a continuing physiological need for nicotine). While nicotine in tobacco has both systemic pharmacological effects and acute sensory effects in the mouth, nose, and throat,[581] the evidence in the preceding sections and other industry documents demonstrates that the acute sensory effects of nicotine are secondary in importance to

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[580] *See:*
Regulation of Tobacco Products (Part 1): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives, 103 Cong. 2d Sess. 763 (April 14, 1994). (testimony of TF Riehl, Vice President for Research & Development, Brown and Williamson Tobacco Corp.):

We blend for taste, not nicotine.

Id. 103 Cong. 2d Sess. 590 (statement of Thomas E. Sandefur, Jr., CEO Brown and Williamson Tobacco Corp.) :

Without nicotine, cigarettes simply would not taste like cigarettes.

Statement of Brennan Dawson, Vice President, Tobacco Institute. *Face the Nation.* March 27, 1994. Page 7:

Nicotine is essential. It has a taste. It has what's called a mouth feel.

[581] *See, e.g.*, Proceedings of the BATCO Smoking Behaviour-Marketing Conference, Session III. Montreal, Canada. July 9-12, 1984. Pages BW-W2-02709, BW-W2-02698. Breaks down smoke sensations into (1) mouth sensations, including mouth feel, texture and taste; (2) sensations on inhalation, including throat feel, irritation, and impact; and (3) wholebody pharmacological and psychological effects.

the pharmacological effects of nicotine that underlie consumer satisfaction. For example, a 1972 Philip Morris document from a Council for Tobacco Research conference addressing the issue of why people smoke makes clear that:

> *The primary incentive to cigarette smoking is the immediate salutory effect of inhaled smoke upon body function . . . . The physiological effect serves as the primary incentive; all other incentives are secondary.*[582] [Emphasis added.]

A nicotine monograph prepared for the Tobacco Advisory Council in the United Kingdom also makes clear that smoking satisfaction is dependent on the inhalation of nicotine.

> *Whilst smoking fulfils [sic] a psychological need in certain individuals it is only the inhaling cigarette smoker who is likely to gain psychopharmacological satisfaction from nicotine and become dependent on it.*[583]

Many industry documents reveal that the industry draws a clear distinction between nicotine's pharmacological effects and any effects it has on flavor. A 1984 letter from a BATCO Group R&D researcher to a Brown and Williamson executive drew the distinction between nicotine's pharmacological effects and the sensory properties of cigarette smoke, underscoring the distinction by pointing out that people inhale cigarette smoke (an act that occurs after any sensory effects of cigarette smoke are felt in the nose, mouth, and throat) in order to obtain nicotine's pharmacological effects on the brain:

> *It is well known that nicotine can be removed from smoke by the lung and transmitted to the brain within seconds of smoke inhalation. Since it is the major or sole pharmacologically active agent in smoke, it must be presumed that this is its preferred method of absorption and thus why people inhale smoke. . . . . The organoleptic [sensory] properties of smoke are more complex since they involve*

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[582] Dunn WL. Philip Morris Research Center. *Motives and Incentives in Cigarette Smoking.* Philip Morris Research Center. Richmond, VA. 1972. Pages 3-4.

[583] Cohen AJ, Roe FJC. *Monograph on the Pharmacology and Toxicology of Nicotine and its Role in Tobacco Smoking.* Tobacco Advisory Council. U.K. July 1979. Page 38.

the stimulation of a variety of areas in the mouth, nose and throat.[584]

At the 1983 BATCO Research Conference in Rio de Janeiro, the industry discussed its understanding that nicotine "satisfaction" comes from inhalation and absorption of nicotine into the bloodstream rather than from its flavor. There was discussion of possible cigarette modifications to reduce inhalation of toxic smoke components and thus reduce smoker health risk. Smoker risk could be reduced (1) by modifying the cigarette to reduce retention of smoke in the lung, or (2) by increasing smoke irritation to reduce depth of inhalation and thus resulting absorption. The conferees were reminded, however, that such modifications, to the extent that they result in decreased nicotine absorption and resulting pharmacological effects, may threaten smoker "satisfaction." They were told that it was therefore essential to pay attention to the amount of nicotine that was inhaled, to determine whether absorption was adequate with less deep inhalation:

> *The basic assumption is that nicotine, which is almost certainly the key smoke component for satisfaction, is fully released to the body system before exhalation takes place. It is essential, therefore to attempt to quantify the change in chemical composition between inhaled and exhaled smoke under different conditions of smoking, ie., shallow, medium and deep inhalation. The absorption of nicotine via the nasal cavity should also be investigated.*[585]

Other BATCO documents also show that the industry treats nicotine's pharmacological

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[584] Ayres CI. BATCO letter to E.E. Kohnhorst, Brown and Williamson, transmitting partial summary of issues presented at Montebello Research Conference in 1982. Page BW-W2-03949. (Summary prepared in 1984.)

See also a BATCO report in which it was hypothesized that "increased smoker response is associated with nicotine reaching the brain more quickly." Backhurst JD. BATCO R&D. *Further Work on "Extractable Nicotine."* Report No. RD 437-R. Southampton, England. September 30, 1966. Page 1.

[585] BATCO Research Conference. Brazil. July 1983. Page 7.

effects as distinct from the flavor characteristics of tobacco.[586] As described in FINDINGS § II.C.1., supra, "Project Wheat" was an industry study intended to aid BATCO in developing cigarettes with increased consumer acceptance.[587] The Project Wheat researchers emphasized the importance of nicotine delivery over all other product features and specifically distinguished the effects of nicotine from the taste and flavor characteristics of cigarettes:

> *In considering which product features are important in terms of consumer acceptance, the nicotine delivery is one of the more obvious candidates. Others include the taste and flavour characteristics of the smoke, physical features such as draw resistance and rate of burn, and the general uniformity of the product, to name but a few. The importance of nicotine hardly needs to be stressed, as it is so widely recognised.*[588] [Emphasis added.]

Even RJR research scientists publicly acknowledge that the nicotine in cigarettes provides pharmacological and psychological effects to smokers in addition to any mere sensory effects.[589] An internal RJR document from 1972 is more explicit in showing that the industry views nicotine's role as pharmacological and distinct from the smoke components that provide flavor:

> *If nicotine is the sine qua non of tobacco products, and tobacco products are recognized as being attractive dosage forms of nicotine, then it is logical to design our product - and where possible our advertising - around nicotine delivery rather than around tar delivery or flavor.*[589a] [Emphasis added.]

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[586] BATCO Group R&D Sydney, Australia. March 1978. Page 6. According to "Notes on Group Research & Development Conference" written by S.J. Green on April 6, 1978, the conferees were asked to assist in developing "an effective means of obtaining a nicotine-rich, and preferably flavour-rich extract from waste tobacco."

[587] *See* Project Wheat - Part 1, note 204, *supra,* at p. 1.

[588] *Id.* at pp. 3-4.

[589] Robinson JH, Pritchard WS. The role of nicotine in tobacco use. *Psychopharmacology.* 1992;108:405.

[589a] Hilts PJ. U.S. Convenes Grand Jury to Look at Tobacco Industry. *New York Times.* July 26, 1995. An internal Philip Morris document similarly reveals the industry's understanding that people smoke for the pharmacological effects of nicotine, not for flavor. Reporting on a survey of the reasons

Industry patents also distinguish the role of nicotine from flavorants.[590] An RJR book on flavoring tobacco lists approximately a thousand flavorants, but fails to list nicotine as a flavoring agent.[591] In fact, nicotine's flavor is unpleasant,[592] and the tobacco industry has gone to significant lengths to mask the flavor of increased levels of nicotine in cigarettes.[593]

Moreover, there is evidence that some of the sensory effects associated with nicotine, e.g., irritation and "impact," are sought by smokers at least in part because these effects are always followed by the pharmacological effects they seek. Thus, smokers learn to associate the sensory impact of nicotine (burning in the throat) with the resulting psychoactive effects of nicotine, and thus look for these sensory signals in tobacco products. This is known as secondary reinforcement.[594] Industry documents show that the industry is aware of this

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people say they smoke, a Philip Morris researcher says that the reasons given fall into three categories: 1) "as a narcotic, tranquilizer, or sedative," 2) at the beginning or end of a basic activity, and 3)automatic smoking behavior. The researcher concludes:

> *It should be noted that there was scarcely any unprompted reference to smoking for "taste," or "flavor," until it was suggested-and then everyone agreed that it was the major element in smoking satisfaction.*

Memorandum from Al Udow, Philip Morris, New York, NY, to Mr. J.J. Morgan. Why People Start to Smoke. June 2, 1976. *In* 141 Cong. Rec. H7665 (daily ed. July 25, 1995).

[590] U.S. Patent No. 3,584,630. Inskeep GE. *Tobacco Product Having Low Nicotine Content Associated with a Release Agent having Nicotine Weakly Absorbed Thereon.* Philip Morris Inc. June 15, 1971. C1:57-58.

[591] Leffingwell JC, Yound HJ. *Tobacco Flavoring for Smoking Products.* Winston-Salem, NC: R.J. Reynolds Tobacco Company; 1972.

[592] Budavari S, O'Neil MJ, Smith A, Heckelman PE, eds. The Merck Index. 11th ed. Rahway, NJ: Merck & Co., Inc. 1989:1030. *The Merck Index* describes nicotine as having "an acrid, burning taste."

[593] *See, e.g.,* U.S. Patent No. 4,830,028. Lawson JW, Bullings BR, Perfetti TA. *Salts Provided from Nicotine and Organic Acid as Cigarette Additives.* R.J. Reynolds Tobacco Company. May 16, 1989. C1. *See also* p. 250 *et seq.*

[594] *See* p. 102. Rose JE, Levin ED. Inter-relationships between conditioned and primary reinforcement in the maintenance of cigarette smoking. *British J. of Addiction.* 1991;86:605-609.

relationship.[595]

The industry's development of nicotine analogues also demonstrates that the industry is more interested in nicotine's pharmacological effects on the central nervous system than in its sensory effects. The focus of industry research has been to develop compounds that will duplicate the pharmacological effects of nicotine on the central nervous system. Nowhere in the referenced tobacco industry documents concerning nicotine analogues is there mention of concern to duplicate any flavor, taste, or other acute sensory effects that may be associated with nicotine. This fact was acknowledged by Dr. DeNoble in his congressional testimony, as evidenced by the following exchange with Congressman Waxman:

> *Waxman: Now, you ran a laboratory that was charged with identifying the essential characteristics of nicotine so that a synthetic form of nicotine could be developed, yet you didn't test for the taste of nicotine. Did you ever hear any serious discussion to the effect that Philip Morris leaves nicotine in cigarettes for taste?*
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> *DeNoble: No, sir. None at all.*[596]

In summary, tobacco industry documents make clear that the industry understands that the pharmacological effects of nicotine explain why there is a market for cigarettes, and why

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[595] BATCO Conference Outline, 1984, note 287, *supra,* at p. BW-W2-01977:
An immediate sensory affect [sic] associated with nicotine is the "impact" on inhaling. Is this sensation a genuine part of the reward a smoker is seeking, or is it a "cue", i.e., a smoker has learnt by experience, that if he perceives a particular level of impact, he will subsequently receive an acceptable degree of satisfaction.

Other BATCO documents refer to a 1969 BATCO study (B-A.T. R. & D.E. Report No. RD.640-R) whose objective was to determine the relationship between "impact" and physiological response. *See, e.g,* BATCO. Relative Contributions of Nicotine and Carbon Monoxide to Human Physiological Response. Nov. 15, 1971. Page 2. RD.640-R was not among the documents provided to Congress by Brown and Williamson.

[596] *Regulation of Tobacco Products (Part 2): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives,* 103 Cong. 2d Sess. 16 (April 28, 1994) (testimony of Victor DeNoble).

nicotine's sensory effects are distinct and quite secondary. Tobacco industry documents concerning nicotine analogues further support the conclusion that the pharmacological effects of nicotine are of much greater importance to the industry than nicotine's sensory effects.

H. INDUSTRY FAILURE TO REMOVE NICOTINE FROM TOBACCO DESPITE AVAILABLE TECHNOLOGY

The tobacco industry has developed, over several decades, technologies to selectively remove nicotine from tobacco. This capability is evidenced by the various patents for methodologies to extract nicotine from tobacco,[597] attempts to market denicotinized cigarettes,[598]

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[597] *See, e.g.:*

U.S. Patent No. 3,139,435. Staley J, Clarke AB. *Process for Selective Extraction of Alkaloid.* Philip Morris Inc. June 30, 1964.

U.S. Patent No. 4,557,280. Gravely LE, Geiss VL, Knobs F, Gregory CF. *Process for Reduction of Nitrate and Nicotine Content of Tobacco by Microbial Treatment.* Brown and Williamson Tobacco Corporation. December 10, 1985.

U.S. Patent No. 3,046,997. Hind JD. *Selective Alkaloid Extraction.* Philip Morris Inc. July 31, 1962.

U.S. Patent No. 4,068,671. Casey WJ. *Nicotine Removal Process.* AMF Inc. January 17, 1978.

U.S. Patent No. 4,821,749. Toft HC, Smith KW, Carpenter CR. *Extruded Tobacco Materials.* R.J. Reynolds Tobacco Company. April 18, 1989.

U.S. Patent No. 5,018,540. Grubbs HJ, Prasad R, Howell TM. *Process for Removal of Basic Materials.* Philip Morris Inc. May 28, 1991.

U.S. Patent No. 5,119,835. Heeman V, Schmekel G, Ebling U, Hauser B, Koene CH, Rabitz H. *Method for Extracting Tobacco Alkaloids.* B.A.T. Cigarettenfabriken GmbH. June 9, 1992.

U.S. Patent No. 4,898,188. Niven Jr BF, Mays CD. *Tobacco Processing.* R.J. Reynolds Tobacco Company. February 6, 1990.

U.S. Patent No. 4,967,771. Fagg BS, Frederickson JD. *Process for Extracting Tobacco.* R.J. Reynolds Tobacco Company. November 6, 1990.

U.S. Patent No. 4,150,677. Osbourne Jr JS, Hartung HA, Bebbs Jr JF. *Treatment of Tobacco.* Philip Morris Inc. April 24, 1979.

U.S. Patent No. 5,065,775. Fagg BS. *Tobacco Processing.* R.J. Reynolds Tobacco Company. November 19, 1991.

European Patent No. 280,817. Grubbs HJ, Prasad H, Howell TM. *Process for Removal of Basic Materials.* Philip Morris Inc. Filed on December 24, 1987.

[598] Citizen Petition submitted by the American Heart Association, the American Lung Association and the American Cancer Society, acting as the Coalition on Smoking OR Health, to the U.S. Food and Drug

and industry practices.[599] Despite these denicotinization methods, the tobacco industry uniformly leaves nicotine, an addictive substance, in cigarettes and smokeless tobacco products at levels that are high enough to maintain a pharmacological response in consumers. See FINDINGS § I.C. The fact that tobacco manufacturers could remove an addictive substance from their products, yet choose to leave nicotine in their products at specified levels, demonstrates the tobacco industry's intent to market products that affect the structure and function of the body.

FDA recognizes that the mere existence of a patent is not confirmation that the patent holder is using the invention claimed in the patent. Evaluation of the type and scope of patent assignments to an individual company does, however, provide evidence of the capabilities and interests of the individual company. Taken as a whole, evaluation of these particular patents demonstrates the tobacco industry's capabilities and technologies available for removing nicotine from tobacco.

Patents assigned to several of the major cigarette manufacturers demonstrate that the industry has been investigating, and has at its disposal, various ways to remove nicotine from tobacco. Many of these patents are for technologies that selectively remove nicotine while maintaining the integrity and utility of the rest of the tobacco.[600]

Administration, requesting Classification of "NEXT" and other DeNicotinized Cigarettes as Drugs under the Food, Drug, and Cosmetic Act. FDA Docket No. 91P-0144, submitted April 8, 1991.

[599] Browne C. *The Design of Cigarettes*. Hoechst Celanese. 1990. Page 43. (The process of manufacturing reconstituted tobacco removes nicotine from the tobacco and most cigarettes contain about 20% reconstituted tobacco.)

[600] *See:*
U.S. Patent No. 3,139,435, note 597, *supra.*

More than 30 years ago Philip Morris was assigned a patent that "relates to an efficient process for selective extraction of nicotine and other alkaloids from tobacco while not materially affecting the content or properties of waxes, aromatics, flavoring, and other constituents of the tobacco."[601] Philip Morris subsequently patented an invention that the company claimed improved prior processes in the ability to extract nicotine from tobacco.[602] The claimed improved invention provided a "simpler and less expensive means for removing nicotine."[603]

R.J. Reynolds also has patented several solvent extraction processes which first produce a tobacco extract and then denicotinize the extract.[604] One particular patent is for a process that removes and then redistributes certain components of a tobacco material.[605] The patent describes the ability to provide a denicotinized tobacco material in which 95% of the nicotine is removed.

A different type of patented extraction process that significantly reduces the nicotine content of tobacco uses ammonia as an exudant. RJR was assigned a patent for this type of denicotinization process.[606]

U.S. Patent No. 3,046,997, note 597, *supra.*
U.S. Patent No. 5,018,540, note 597, *supra.*
U.S. Patent No. 4,967,771, note 597, *supra.*
U.S. Patent No. 4,068,671, note 597, *supra.*

[601] *See* U.S. Patent No. 3,046,997, note 597, *supra.*

[602] *See* U.S. Patent No. 3,139,435, note 597, *supra.*

[603] *Id.* at C:51-52.

[604] *See* U.S. Patent No. 4,967,771, note 597, *supra,* at C2:31-33. (Provides for the removal of greater than 95% weight percent of the nicotine.)

See also U.S. Patent No. 5,065,775, note 597, *supra.*

[605] *Id.* U.S. Patent No. 5,065,775, C1:39-43.

[606] *See* U.S. Patent No. 4,821,749, note 597, *supra.*

Several cigarette manufacturers, including Philip Morris, BATCO, and RJR, have been awarded patents over the last 5 years for supercritical extraction[607] procedures that can selectively remove nicotine from tobacco.[608] In a Philip Morris patent for a supercritical extraction process, the patent states that one of the objects of the invention is transferring "nicotine from one tobacco substrate (leaf material or reconstituted leaf) to a second tobacco substrate (leaf material, reconstituted leaf material, or tobacco stems) or to a non-tobacco substrate."[609] An RJR patent describes the company's patented process for extracting tobacco components from tobacco material for transfer to a "smokable material" that is "suitable for use and/or processing for the manufacture of . . . cigarettes."[610] The component to be extracted, as claimed in the patent, is nicotine.[611]

Brown and Williamson and its parent company, BATCO, have patented several processes

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[607] Supercritical extraction processes use solvents that are in their supercritical state. This means that the solvent is above its critical point with respect to temperature and pressure. (U.S. Food and Drug Administration. Center for Food Safety and Nutrition. Office of Plant & Dairy Foods and Beverages. Division of Natural Products. What is Supercritical Fluid? Standard Guide for Supercritical Fluid Chromatography Terms and Relationships.) Most of the patents use carbon dioxide (CO_2) as the solvent. As described in one of the patents, critical CO_2 occurs when the CO_2 temperature is above its critical temperature of 31.3° C in its gaseous phase under high pressure, e.g., 70 to 1500 atmospheres pressure. U.S. Patent No. 4,153,063. Roselius W, Vitzthum O, Hubert P. *Process for the Extraction of Nicotine from Tobacco.* Studiengesellschaft Kohle mbH. May 8, 1979. C-1.

[608] *See:*
U.S. Patent No. 5,018,540, note 597, *supra.*
U.S. Patent No. 5,119,835, note 597, *supra.*
U.S. Patent No. 4,153,063, note 607, *supra.*
U.S. Patent No. 4,898,188, note 597, *supra.*
European Patent No. 280,817, note 597, *supra.*

[609] *See* U.S. Patent No. 5,018,540, note 597, *supra,* at C2:39-43.

[610] *See* U.S. Patent No. 4,898,188, note 597, *supra,* at C5:12-14.

[611] *Id.* at C9:10-11.

for denicotinizing tobacco by exposing the tobacco to microbes.[612] The processes in these patents are based on the recognition that when tobacco is inoculated with certain types of microorganisms for a specified period of time the nicotine is degraded. The longer the tobacco is exposed to the microorganism, the more nicotine is degraded.

Further evidence of the ability of the tobacco industry to remove nicotine is seen in the marketing of a cigarette that was advertised as "de-nicotined." In 1989, Philip Morris test-marketed a cigarette, NEXT, that contained less than 0.1 milligrams of nicotine. The company's own advertisements for NEXT announced that a process called the "FreePLUS" system "naturally extract[s] nicotine from fine tobaccos, . . . with rich tobacco flavor and less than 0.1 mg nicotine."[613] This product was withdrawn from the market shortly after it was introduced for test-marketing.

Despite this arsenal of nicotine-removing technologies, all brands of currently marketed cigarettes contain levels of nicotine that are sufficient to maintain a pharmacological response in smokers. Although cigarette manufacturers have the ability to market denicotinized tobacco products, to date there has not been any serious attempt, except for NEXT cigarettes, to market these types of products. All cigarettes on the market today have, and deliver, levels of nicotine

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[612] *See:*
U.S. Patent No. 4,557,280, note 597, *supra.*

U.S. Patent No. 4,037,609. Newton RP, Geiss VL, Knobs F, Jewell JN, Gravely LE. *Process for Reduction of Nicotine Content of Tobacco by Microbial Treatment.* Brown and Williamson Tobacco Corporation. July 26, 1977.

U.S. Patent No. 4,038,993. Geiss VL, Knobs F, Gregory CF, Newton RP, Gravely LE. *Process for Reduction of Nicotine Content of Tobacco by Microbial Treatment.* Brown and Williamson Tobacco Corporation. August 2, 1977.

[613] Package label for NEXT brand cigarettes.

that maintain an addiction to the product. These levels are deliberately maintained by the manufacturers. Because tobacco manufacturers can control the amount of nicotine, and even remove nicotine altogether if they choose, it is evident that manufacturers intend to market cigarettes and smokeless tobacco products that affect the structure and function of the body.

PART THREE: REGULATORY OBJECTIVES

Smoking and other tobacco use is the single leading cause of preventable death in the United States. Each year, over one million children and adolescents begin using tobacco products. Most eventually become addicted. Any program devised by the Agency should be comprehensive, effective, and designed to prevent young people from experimenting with and becoming addicted to nicotine.

Currently 3 million young people are regular smokers and another 1 million use smokeless tobacco.[614] Every day another 3,000 children and teenagers become regular smokers.[615] Although adult rates continue to decline, the prevalence of smoking by young people has not declined for the last decade.[616] In fact, between 1992 and 1993, the prevalence of smoking among high school seniors increased from 17.2% to 19%.[617] Additionally, smoking among college freshmen increased from 9% in 1985 to 12.5% in 1994.[618] However, by the time

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[614] U.S. Department of Health and Human Services. Preventing Tobacco Use Among Young People: A Report of the Surgeon General. 1994. Page 58.

[615] Institute of Medicine. Growing Up Tobacco Free: Preventing Nicotine Addiction in Children and Youths. National Academy Press. 1994. Page 5.

[616] *See:*
CDC. Cigarette Smoking Among Adults - United States, 1993. *MMWR.* 43:925-930. Dec. 23, 1994.

U.S. Department of Health and Human Services. Reducing the Health Consequences of Smoking: 25 Years of Progress, A Report of the Surgeon General. 1989. Page 269.

Institute of Medicine. Growing Up Tobacco Free: Preventing Tobacco Addiction in Children and Youths, *supra* at pp. 7-8.

[617] The University of Michigan. Monitoring the Future Study. January 27, 1994. Table 1 - "Trends in Prevalence of Various Drugs for Three Populations: Eight, Tenth, and Twelfth Grades."

[618] Washington Post, January 9, 1995. Page A2, col. 3.

young people are smoking regularly, they already regret having started.[619] A 1992 Gallup Survey confirmed this, showing that 70% of regular adolescent smokers regretted having begun to smoke and wished they could quit. If an adolescent's cigarette or smokeless tobacco use continues into adulthood, he or she may ultimately become one of the over 400,000 Americans who die from tobacco-caused diseases each year.[620]

Most adult smokers became regular smokers as youngsters. Among those adults who ever smoked regularly, nearly 90% began to smoke, and more than 70% became regular smokers, by age 18.[621] It is clear, therefore, that if smoking does not begin in childhood or adolescence, it is unlikely that it will ever begin. Thus, addiction to nicotine-containing tobacco products is, first and foremost, a pediatric disease.

FDA regulatory action should be based on a youth-centered strategy that is intended to reduce the risk that future generations of Americans will become dependent on nicotine without prohibiting access to these products by adults. The Agency recognizes the need for cigarettes and smokeless tobacco products to remain available to adults, because millions of American adults use and are addicted to these products. The potential disruption to society resulting from the elimination of tobacco products would be great, and therefore FDA does not intend to remove them from the market.

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[619] George A. Gallup International Institute. Teenage Attitudes and Behavior Concerning Tobacco - Report of the Findings. Princeton, New Jersey. 1992.

[620] U.S. Department of Health and Human Services. Reducing The Health Consequences of Smoking: 25 Years of Progress, A Report of the Surgeon General. 1989. Page 5.

[621] U.S. Department of Health and Human Services, Preventing Tobacco Use Among Young People, A Report of the Surgeon General, *supra,* at pp. 63-65.

A comprehensive and effective regulatory approach should be designed to reduce the many avenues of easy access to tobacco products available to children and teenagers, and to make it harder for young people to buy these products. The Agency should also act to reduce the powerful and alluring imagery used in tobacco advertising and promotion that tends to encourage impressionable young people to initiate tobacco use, and should attempt to enhance the positive image of a smoke-free generation. Further, such actions should seek to educate people about the specific and relevant health risks associated with tobacco use and to disseminate information about quitting.[622]

[622] The issues discussed in the "Regulatory Objectives" section were also addressed by David A. Kessler, M.D., Commissioner of Food and Drugs, in a speech at the Columbia University School of Law on March 8, 1994. A copy of the speech appears in Appendix 9.

Dated: August 8, 1995.

David A. Kessler,

Commissioner of Food and Drugs.

[FR Doc. 95–20052 Filed 8–10–95; 8:45 am]

BILLING CODE 4160–01–C