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.