

**COMMENTS OF PHILIP MORRIS INCORPORATED**  
**ON**  
**STATEMENTS FILED BY FDA ON MARCH 18, 1996**

Docket Nos. 95N-0253, 95N-0253J

April 19, 1996

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BEFORE THE  
UNITED STATES FOOD AND DRUG ADMINISTRATION  
DOCKET NOS. 95N-0253, 95N-0253J

COMMENTS OF PHILIP MORRIS INCORPORATED  
ON STATEMENTS FILED BY FDA ON MARCH 18, 1996

The Agency has reopened the comment period on its analysis regarding purported FDA jurisdiction over "nicotine-containing" cigarettes to permit comments on "declarations" from three former Philip Morris employees that "FDA might rely on . . . in support of any final decision it might make on its jurisdiction." 61 Fed. Reg. 11,419 (March 20, 1996).<sup>1</sup> According to the Agency, these declarations describe "the industry's understanding of nicotine and industry practice with respect to the control of nicotine levels in cigarette manufacture." *Id.*

As described below, in the accompanying comments of the industry as a whole, and in the comments previously filed on January 2, 1996, a great many of the factual propositions

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<sup>1</sup> Philip Morris contends that FDA's assertion of jurisdiction over cigarettes and the initiation of this rulemaking are an unlawful usurpation of authority that Congress has reserved to itself or delegated to other state and federal agencies. Philip Morris, along with other manufacturers, has filed a legal action against this proceeding. By submitting these comments, Philip Morris does not waive its objection to FDA's authority to proceed with this rulemaking.

contained in these three belated declarations are either wrong or seriously misleading.<sup>2</sup>

I. THE LEGAL IRRELEVANCY OF THE DECLARATIONS

The bulk of these comments will address the factual invalidity of the various statements made in the three declarations. We would, however, be remiss if we did not note at the outset that, even if all of the assertions in the three declarations were true (and they are not), and even if they constituted competent evidence based on personal knowledge (and they do not), they are still legally irrelevant to the issue of FDA jurisdiction over cigarettes. (Dkt. Nos. 95N-0253; 95N-0253J; 60 Fed. Reg. 42,314, et seq. (Aug. 11, 1995)). Neither Philip

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<sup>2</sup> Philip Morris requested that the Agency extend the comment period by 17 days to permit the company to present additional information in response to the declarations, including testimony from the depositions of two of the three former employees. The Agency, however, has refused to grant such a brief extension -- notwithstanding that its staff apparently worked to secure the declarations for many months and then withheld them from the public docket for some additional time. Philip Morris therefore reserves the right to supplement these comments should additional information concerning these "declarations" come to light in the near future.

The Agency has further advised that it will consider only information directly responsive to the declarations and that commenters should not restate information contained in prior submissions. Philip Morris has followed these directions and therefore has not restated all of the information in its prior individual submission and the joint industry comments filed on January 2, 1996 which already address much of what is recycled in the "new" declarations. Obviously the Agency must also consider all of those prior comments when it evaluates the "new" declarations; and Philip Morris hereby incorporates those prior comments by reference.

Morris' general knowledge about nicotine -- including any research it may have performed to obtain that knowledge -- nor its internal manufacturing procedures constitutes relevant evidence that the nicotine in its cigarettes, which is naturally-occurring, or the cigarettes themselves, are "drugs" or "devices" subject to FDA jurisdiction.

Under the Federal Food, Drug, and Cosmetic Act ("FDCA"), a product is a drug or medical device only if it is "intended for use" in diagnosing, treating or preventing disease, or is "intended to affect" the structure or any function of the body. 21 U.S.C. §§ 321(g)(1)(drugs), 321(h)(devices). Given the plain language of the FDCA, as well as its legislative history, the courts have consistently held that a finding that a product is "intended for use" in some therapeutic way or is "intended to affect" the body can be based only upon the objective intent of the manufacturer as determined by the claims and representations made in marketing the product. No court has ever held that a product is a "drug" or "device" in the absence of such claims of therapeutic or significant physiological effect made in connection with its sale.

A product thus may not be regulated by FDA as a "drug" or "device" by virtue of its physical or pharmacological characteristics, the extent of a company's "understanding" of the product or its constituents, or the methods by which it is designed or manufactured. See, e.g., National Nutritional Foods Assoc. v. Mathews, 557 F.2d 325, 336 (2d Cir. 1977); United

States v. An Article of . . . Consisting of 216 Individually  
Cartoned Bottles . . . Sudden Change, 409 F.2d 734, 739 (2d Cir.  
1969); United States v. Two Plastic Drums of an Article of Food,  
791 F. Supp. 751, 752-53 (C.D. Ill. 1991), aff'd, 984 F.2d 814  
(7th Cir. 1993).

Indeed, as described in greater detail in the Industry  
Comments, FDA's own regulations defining "intended use" correctly  
focus on the manufacturer's public expressions -- primarily  
labeling and advertising -- and the circumstances surrounding the  
public distribution of a product. 21 C.F.R. § 201.128 (drugs);  
21 C.F.R. § 801.4 (devices).<sup>3</sup> Those regulations say nothing about  
how a product is designed or manufactured; what ingredients are  
present; what research has been conducted; or the views of  
individual employees about any of these subjects. Such matters  
are simply not legally relevant to the objective "intended use"  
for which a product is promoted or distributed.

Such objective intent under the FDCA may be proved only by  
what the manufacturer or vendor communicates to customers in  
connection with the sale or distribution of the product.<sup>4</sup> As one  
court held in the specific context of cigarettes, "the crux of FDA  
jurisdiction" is predicated on the "manufacturers'  
representations . . . in connection with [a product's] sale," "as

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<sup>3</sup> Comments of Brown & Williamson Tobacco Corporation, Liggett  
Group Inc., Lorillard Tobacco Company, Philip Morris Incorporated,  
R.J. Reynolds Tobacco Company, Tobacco Institute Inc. ("Industry  
Comments") at II-9 to II-14 (Jan. 2, 1996).

<sup>4</sup> Industry Comments at II-5 to II-33.

revelatory of their intent." Action on Smoking and Health v. Harris, 655 F.2d 236, 238-39 (D.C. Cir. 1980). See also E.R. Squibb and Sons, Inc. v. Bowen, 870 F.2d 678, 683 (D.C. Cir. 1989); Sudden Change, 409 F.2d at 739. The courts "have always read the . . . statutory definitions employing the term 'intended' to refer to specific marketing representations." American Health Prods. Co. v. Hayes, 574 F. Supp. 1498, 1505 (S.D.N.Y. 1983), aff'd, 744 F.2d 912 (2d Cir. 1984).<sup>5</sup>

It is likewise clear that in making this determination, the Agency is limited to current marketing claims. Most recently, in United States v. Articles of Drug for Veterinary Use, the court of appeals observed that

"[p]romotional materials are relevant to intent so long as they are currently being distributed with the product, and if not, there must be evidence that customers are still relying on the representations made in promotional materials distributed in the past . . . ." 50 F.3d 497, 500 (8th Cir. 1995) (emphasis added).

The only promotional materials that are relevant to "intended use" are thus those that continue to influence customers. A fortiori, information that has never reached any customer -- internal discussions between company employees regarding research or manufacturing techniques -- are irrelevant to the issue of the product's "intended use."

<sup>5</sup> Accord: Estee Lauder, Inc. v. FDA, 727 F. Supp. 1, 2 (D.D.C. 1989); Hanson v. United States, 417 F. Supp. 30, 34 (D. Minn.), aff'd, 540 F.2d 947 (8th Cir. 1976); United States v. Nutrition Serv., Inc., 277 F. Supp. 375, 386 (W.D. Pa. 1964), aff'd, 347 F.2d 233 (3d Cir. 1965).

Indeed, the declarations of the three former Philip Morris employees demonstrate why statements of individual employees not made in connection with the sale or distribution of a product are not relevant evidence of "intended use." Such statements call to mind the Supreme Court's admonition that, under the FDCA, anecdotal evidence is totally unreliable and can be "treacherous." Weinberger v. Hynson, Westcott and Dunning, Inc., 412 U.S. 609, 619 (1973).

In short, the declarations now at issue themselves make clear that none of the personal views or internal discussions they purport to relate -- assuming they took place at all -- were ever communicated to consumers in conjunction with the sale of any Philip Morris cigarettes. For that reason alone, they are legally irrelevant. And, as we shall now show, they are factually invalid as well.

## II. THE UYDESS DECLARATION

The longest of the three declarations is from Dr. Ian Uydess, an associate research scientist who worked at Philip Morris at various times between 1977 and 1989. During his tenure at Philip Morris, Dr. Uydess, a cell biologist, worked with the physical and biological properties of tobacco. His declaration indicates that much of his "understanding" of the other Philip Morris activities he purports to describe -- such as research related to the effects of nicotine -- was derived from colleagues who shared their "experiences" during coffee breaks.

Perhaps most importantly for present purposes, Dr. Uydess had no role in the formulation of any brand of Philip Morris cigarettes, much less with Philip Morris' marketing of those products. Nor, of course, can Dr. Uydess say anything about what has transpired at the company over the last seven years -- and thus his "understandings" are outdated at best.

Quite apart from all of these problems, Dr. Uydess' speculative charges are simply not true. In the pages that follow, we respond to his allegations, more or less in the order in which they were presented.

**A. Nicotine And The Design  
Of Commercial Cigarettes**

At various points in his declaration (Paragraphs 7-15, 21), Dr. Uydess states that "to the best of [his] knowledge" "nicotine has always been an important consideration to Philip Morris in the design, development and manufacturing of cigarettes." This overt hedging by Dr. Uydess -- which occurs at the beginning, middle, and end of his declaration -- is significant because, in fact, he was not involved in the design of Philip Morris' commercial cigarettes. Nor was he involved in any research that focused on nicotine, except, as described below, to the extent he reviewed work on the possible development of a low nicotine species of tobacco.

It is thus quite telling that at no point in his declaration does Dr. Uydess ever identify any specific Philip

Morris cigarette that was "targeted" or "manipulated" to achieve some preordained nicotine yield. To be sure, he speculates that "[w]henver nicotine, or any other major component (such as sugars, tars, etc.) had to be adjusted by Philip Morris in a new or existing product, it was frequently a matter of knowing which tobaccos to use in the blend to make the necessary (targeted) adjustments." Uydess Declaration at 8. But in making such a vague and general statement, Dr. Uydess fails to provide any specifics that would demonstrate that Philip Morris ever attempted to maintain (much less increase) nicotine levels independently of those other well-known natural constituents of tobacco. Rather, he confuses the issue by recounting snippets of what he claims to have overheard during coffee breaks and then leaves the reader to draw some illicit conclusion. The facts, however, show just how invalid his generalized speculations are.<sup>6</sup>

For example, in Paragraph 12 of his declaration, Dr. Uydess notes that Philip Morris scientists understood that nicotine had something to do with a cigarette's "impact". Dr. Uydess concedes that the term "impact" relates to "the feeling that the smoker experiences at in [sic] the back of the throat immediately upon inhaling a nicotine-containing cigarette." Uydess Declaration at 12. Philip Morris agrees with that definition and with the well-known fact that nicotine, in addition to imparting a taste

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<sup>6</sup> Tobacco blending -- the only "technique" cited by Dr. Uydess to support his general claim of "nicotine targetting" -- is addressed at length in the Industry Comments at IV-65 to IV-72.

sensation on the tongue and an aroma sensation in the nose, has such an effect on the back of a smoker's throat -- a sensation that many smokers desire (just as many consumers enjoy the throat "impact" of hot peppers or carbonated soft drinks).<sup>7</sup>

Philip Morris, however, disputes Dr. Uydess' alternative contention that the term "impact" is also "used by the tobacco industry" to describe a second "somewhat more complicated (and delayed) physiological effect which apparently results from the interaction of nicotine with receptor sites in the brain." Uydess Declaration at 12. It is significant that Dr. Uydess does not provide any specifics to support his very different alternative interpretation of the term.

In Paragraph 13 of his declaration, Dr. Uydess similarly obscures the issue of nicotine's contribution to the acceptability of a cigarette in describing an internal meeting at which disappointing test market results of a low-yield cigarette were discussed. He notes that some consumers had reported that the new product was "missing something." Uydess Declaration at 12. Yet, even Dr. Uydess must acknowledge that the particular product under discussion was a low-"tar", as well as a low-nicotine, cigarette -- and that "tar", as well as "tar"-to-nicotine ratios, "were also discussed" at the meeting he apparently attended. Id. at 12-13.

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<sup>7</sup> See Industry Comments at III-112 to III-121.

The fact that Philip Morris employees may have noted the lower yields of "tar" and nicotine in connection with the commercial failure of a low-yield product is, of course, hardly surprising. As described in greater detail in the Industry Comments, those inside (as well as outside) the industry have long known that both "tar" and nicotine contribute to the flavor of a cigarette and that, as a general rule, a low-"tar"/low-nicotine product will have less flavor. Industry Comments at III-112 to III-121. But such a general discussion can hardly be extrapolated, even by Dr. Uydess, to argue that people smoke "nearly exclusively" for the pharmacological effect of nicotine, that the contribution of "tar" and other flavors to the smoking experience is irrelevant, or that those at Philip Morris who discussed this particular low-"tar"/low-nicotine product accepted either of those extreme propositions.

At various points Dr. Uydess does suggest that he is generally aware of some relationship between nicotine yields and consumer acceptance of particular cigarettes. But here too his vague recollections and speculations simply cannot withstand scrutiny.

For example, in Paragraph 14 of his declaration, Dr. Uydess refers to a graph he apparently saw "during an informal discussion at Philip Morris that generally correlated nicotine level to product acceptability." Uydess Declaration at 13. He concedes that this graph did not (as some anti-tobacco critics have suggested) predict a direct relationship between nicotine yield

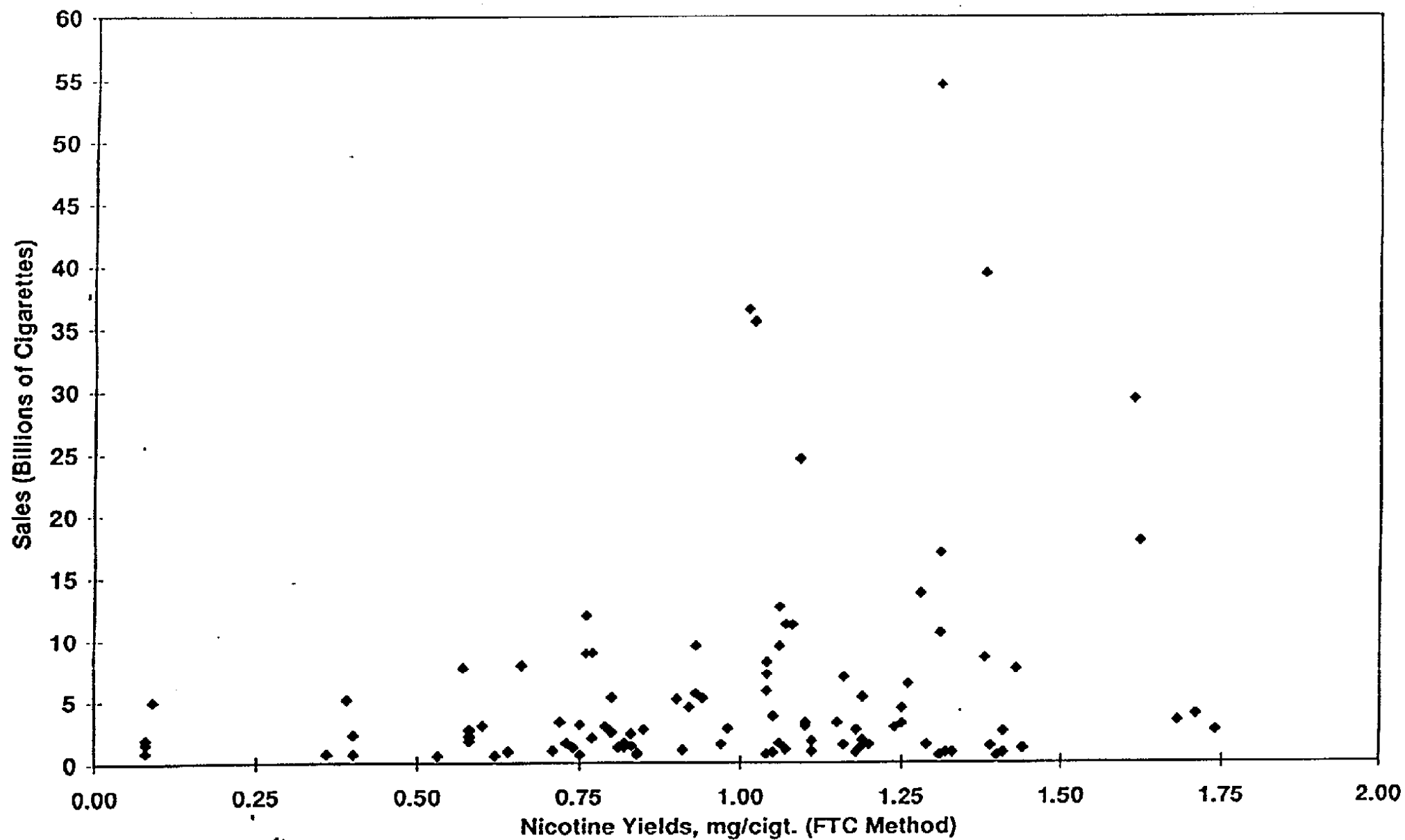
and sales, such that sales continue to increase as nicotine yields increase -- as one would predict if people truly "smoke for nicotine." Rather, Dr. Uydess recalls that the informal graph showed that there was a "high" as well as a "low" limit which indicated "at least in a general manner, the range of nicotine levels over which adequate product acceptability (market share) was believed to occur." Uydess Declaration at 13.<sup>8</sup>

Yet actual market share data -- rather than some "informal" graph Dr. Uydess may have seen ten or fifteen years ago -- do not support the notion that, even within some "general" middle range, a cigarette's sales can be predicted by its nicotine yield. As the following charts demonstrate, whether one selects 1977 (the year Dr. Uydess came to Philip Morris), 1989 (the year he left), or 1995 (the last year for which FTC test data are available), one cannot predict a cigarette's sales failure or success based on nicotine yields.

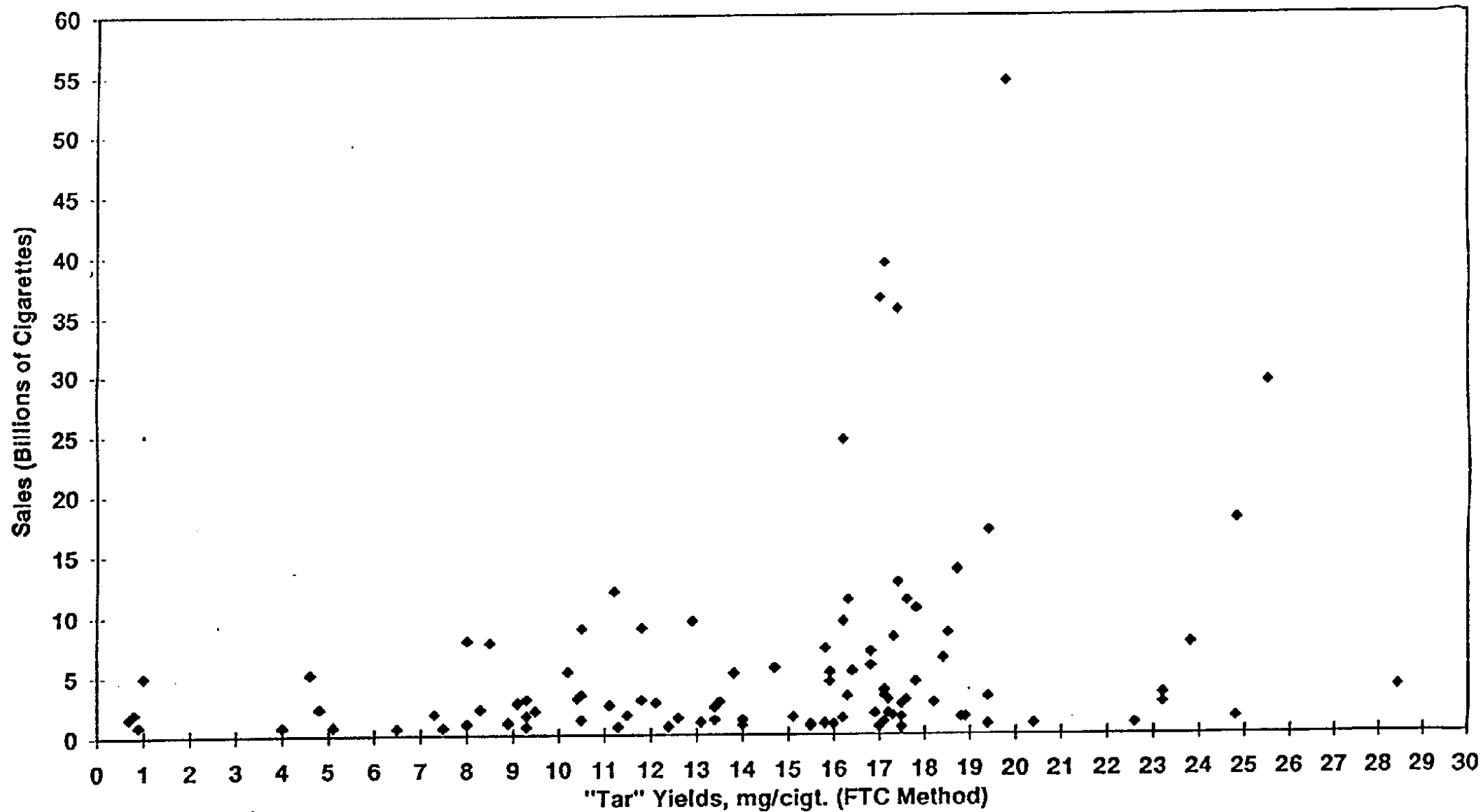
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<sup>8</sup> Although Dr. Uydess then drops any further reference to the upper limit on nicotine yields and smoker acceptance, his recollection is that a cigarette which yields too much nicotine was also likely to be unacceptable to smokers. The Agency's jurisdictional theory, by contrast, would suggest that a "nicotine delivery device" would be all the more acceptable to consumers as nicotine levels increased -- or, at least, that all products would be equally acceptable above a certain "minimum threshold." As even Dr. Uydess recognizes, that is simply not the case.

1977

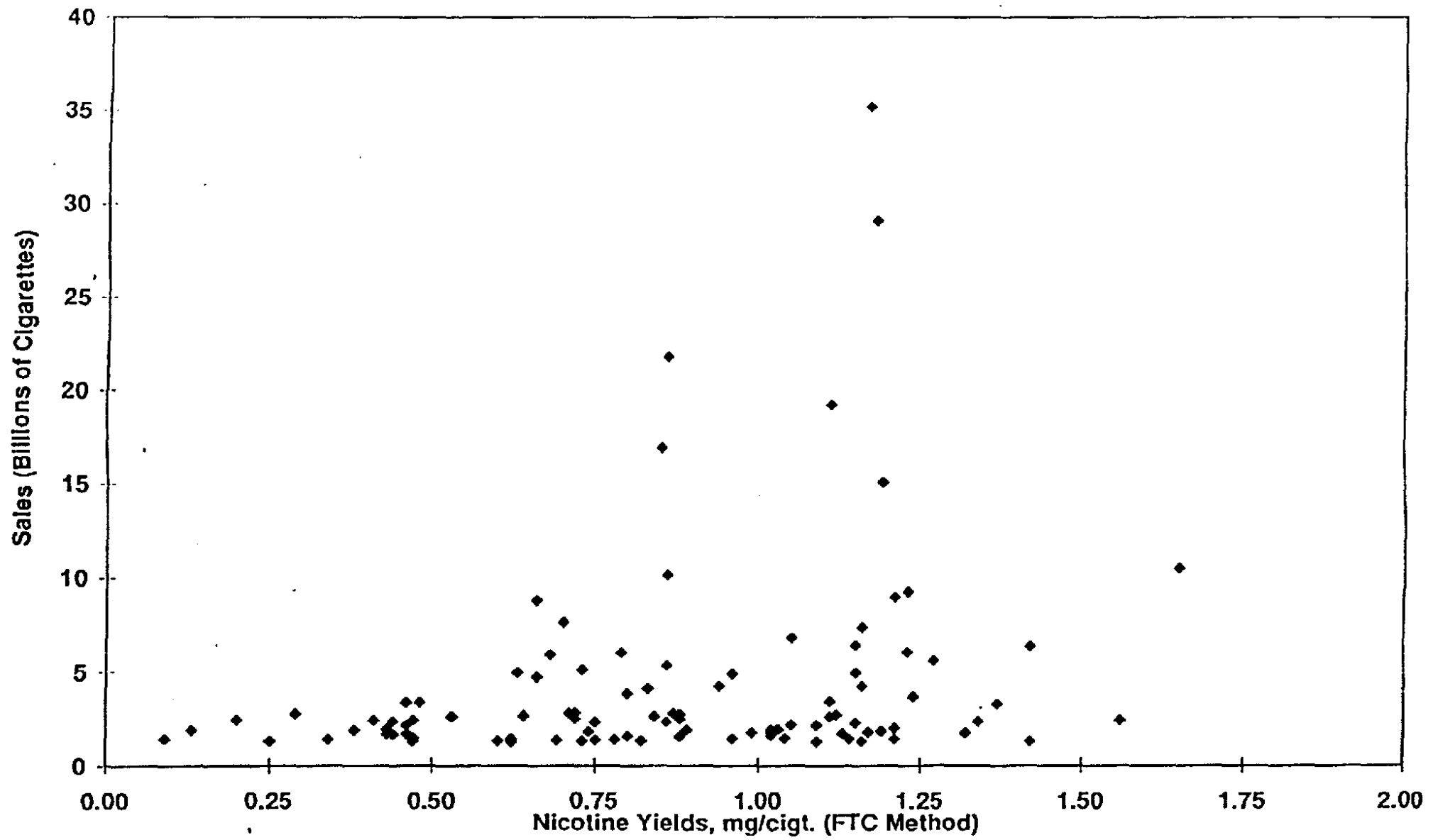


1977



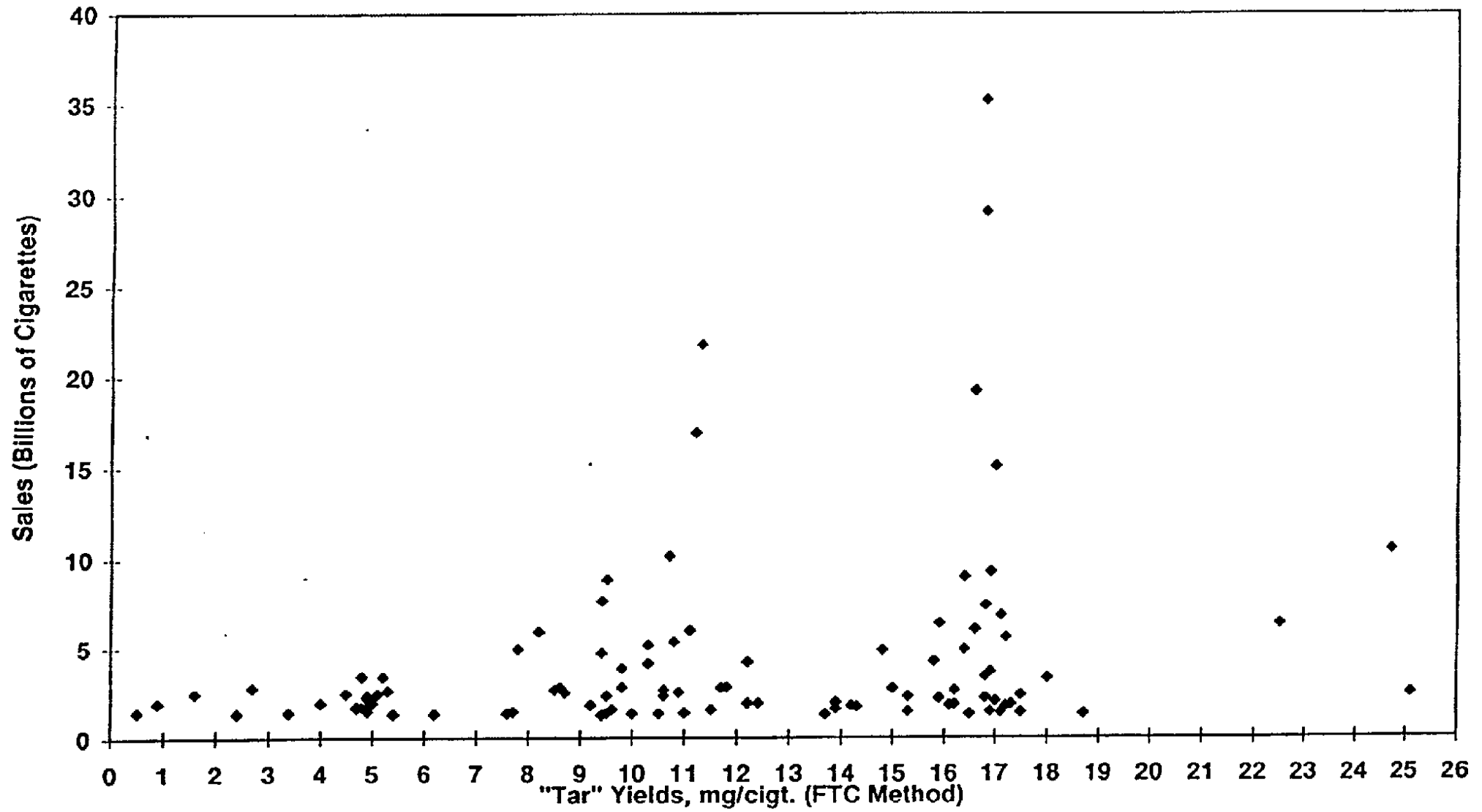
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1989

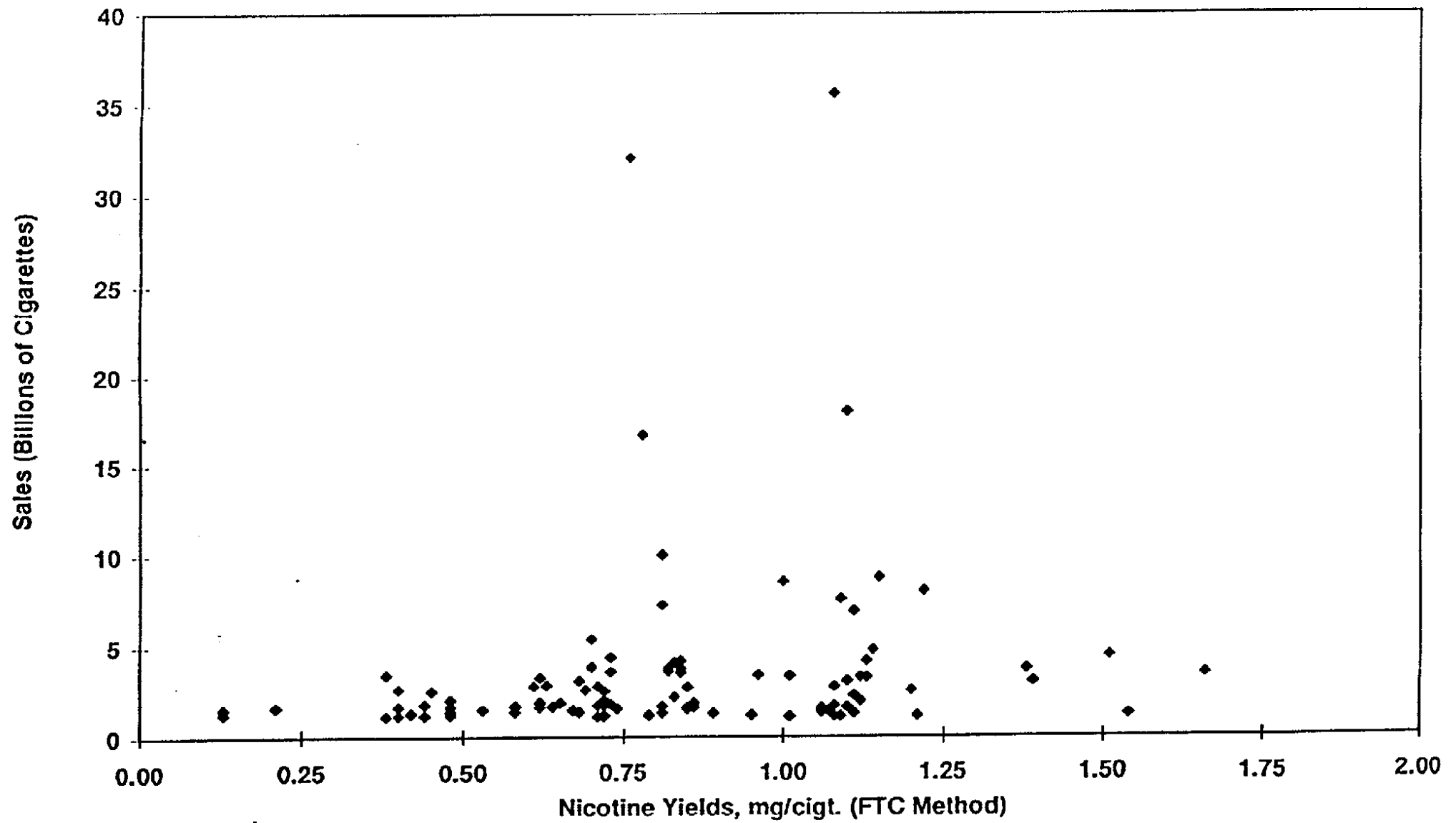


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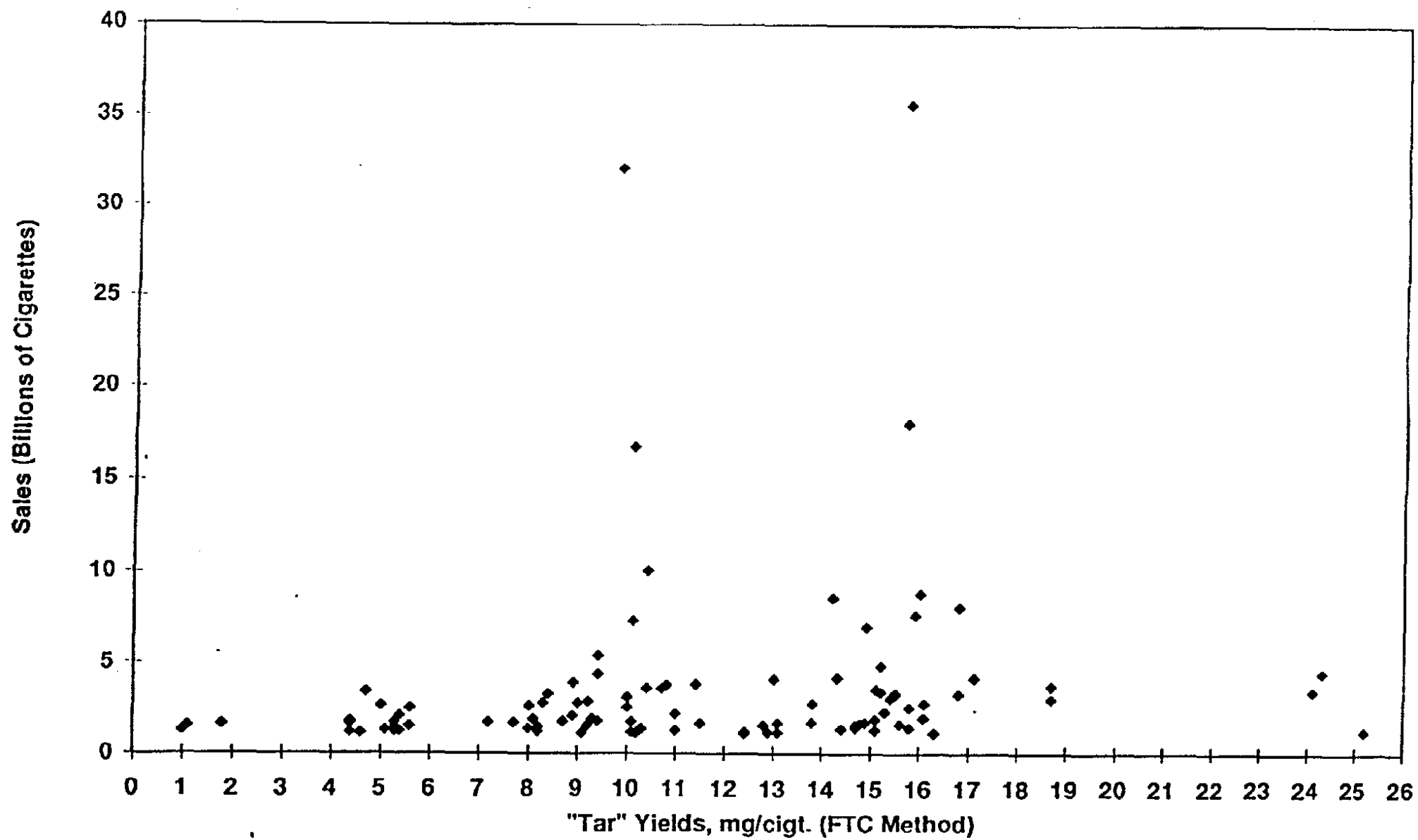
1989



1995



1995



As these scatter-plots plainly show, while there are successful brands in the middle nicotine ranges, other products with exactly the same nicotine yields fare very poorly in the marketplace. Clearly, cigarette consumers make their purchasing decisions on the basis of attributes other than nicotine yields.

Conversely, the success of a number of brands with far lower nicotine yields -- brands which, in many cases, are far more successful than brands with higher, supposedly "optimal" nicotine yields -- confounds any attempt to predict sales on the basis of nicotine yields. For example, as early as 1977, TRUE, a cigarette manufactured by Lorillard, had achieved the rank of 32nd among the 152 packages for which data was available, even though it yielded only .39 mg of nicotine.<sup>9</sup> TRUE thus substantially outsold more than 100 other brand-packages that had higher nicotine yields -- including many with the "magic" level in the middle range suggested by Dr. Uydess. Similarly, in 1989 Reynolds sold substantial numbers of a version of its NOW cigarette (48th on the list of 293 brand-packages) despite the fact that those cigarettes yielded only .2 mg of nicotine. That same year American's ultra-low yield Carlton 100s (.13 mg nicotine yield) ranked 64th out of 293 brand-packages for which data was available.

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<sup>9</sup> The sales information -- and brand rankings -- are taken from the Management Science Associates ("MSA") database. That database provides sales figures as reported to MSA by each manufacturer. Each different package (e.g., soft-pack, hard-pack, king-size) for each different brand name (e.g., Marlboro) is given a separate ranking.

The success of low, and even ultra-low, cigarettes is even more true today. For example, in 1995, Doral Ultra Lights 100 ranked 27th among 457 brands for which data was available -- that is, it outsold more than 90% of the brands on the market -- even though it yielded only .38 mg of nicotine per cigarette. Philip Morris' own Merit Ultra Lights, which yields only .44 mg of nicotine per cigarette, similarly ranked 54th and outsold Philip Morris' regular Merit brand-package (58th) which yielded more nicotine (as well as more "tar"). And the continued sales of such ultra-low brands as Carlton (ranking 67th among the 457 brand-packages), with barely detectable nicotine yields, continue to confirm that cigarettes are sold across the whole spectrum of nicotine yields.

The point, of course, is not to dispute the fact that most cigarettes, including the most popular brands, fall within a broad "middle range" in terms of their "flavor" or "strength" -- just as most people prefer peppers that are neither too spicy, nor too bland, and apples that are neither too tart, nor too sweet. But, as these scatter-plots clearly demonstrate, the same cigarettes fall within a similar middle range in terms of their "tar" yields as well, because "tar" and nicotine are so closely linked. Neither the Agency nor Dr. Uydess has any evidence to suggest that consumers are preferring those products because they are in some broad mid-range in terms of their nicotine yields as opposed to the fact that they are equally in the mid-range of "tar" and hence overall flavor or "strength".

Moreover, as a result of changing tastes of American consumers and the response of manufacturers to those changing tastes, both the overall sales-weighted yields of "tar" and nicotine, and the specific profiles of the most successful brands, have declined over time. Compare charts for 1977, 1989, and 1995 which show a shift to lower "tar" and nicotine yields. This undeniable fact is further evidence that the cigarette manufacturers are not increasing (or even assiduously maintaining) nicotine yields, as one would expect if they truly accepted the proposition that higher nicotine yields mean higher sales.

Indeed, even Dr. Uydess does not suggest that his views, which he may have gleaned from an informal graph shown at a coffee break, on the relationship between nicotine yields and sales was somehow Philip Morris corporate policy. As he acknowledges, "[s]ome participants at this meeting forwarded the idea that the flavor group could overcome these 'problems', while others held fast to their belief that the data 'spoke for themselves.'"

Uydess Declaration at 13. In this respect, Dr. Uydess' declaration is thus entirely consistent with the statements previously made by Philip Morris that various individuals at the company believed that people smoke for many reasons, not solely for nicotine; that others at Philip Morris who, unlike Dr. Uydess, actually develop new cigarettes, therefore work very hard on flavor substitutes to create acceptable low-"tar" and low-nicotine products; and that Philip Morris has not "manipulated" the nicotine yields of its commercial cigarettes.

Finally, Dr. Uydess has failed to put Philip Morris' nicotine-related research, especially with respect to the theoretical possibility of cigarettes with altered nicotine yields, into a proper historical context. He forgets (or perhaps never knew) that a number of government officials and non-industry scientists in the 1970s advocated the development of a cigarette with higher-than-average nicotine-to-"tar" ratios. These proponents of a low-"tar"/high-nicotine cigarette suggested that the American manufacturers investigate the possibility of such a cigarette.

For example, in 1977 the National Institutes of Health, through the Smoking and Health Program of the National Cancer Institute, reported that NCI would study experimental low-"tar" cigarettes with "relatively high" nicotine yields:

"Consideration is being given to the design of experimental low tar cigarettes yielding relatively high nicotine. . . . Designs being considered involve cigarettes with tar/nicotine ratios less than 10. Several problems are being considered; e.g., the source and nature of the nicotine to be used, the role of extenders to influence nicotine delivery, safety of extenders and the type of tests that should be conducted."<sup>10</sup>

Similarly, in 1976 researchers funded by the American Cancer Society recommended that smokers be "encourage[d] to switch to cigarettes with a high yield of nicotine relative to tar and

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<sup>10</sup> *Smoking and Health -- Status Report December 1977*. National Cancer Institute, National Heart, Lung and Blood Institute, National Institutes of Health 33 (1978). (This article and all other articles cited in these comments are provided in the accompanying Appendices.)

carbon monoxide."<sup>11</sup> The ACS researchers publicly thanked Philip Morris for providing experimental cigarettes used in their study.<sup>12</sup> As described by the ACS researchers, these were "special cigarettes yielding amounts of nicotine and tar that are not correlated."<sup>13</sup> Clearly, Philip Morris did not try to hide the fact that it had assisted the ACS researchers in such an investigation of the theoretical possibility of creating experimental cigarettes with altered nicotine-to-"tar" ratios.

Last, but certainly not least, the Surgeon General himself in 1981 advocated research into the development of a low-"tar"/medium-nicotine cigarette:

"It is necessary to evaluate cigarettes with lower tar to nicotine ratios than are currently found in the market place. . . . A low ratio might be a desirable strategy for lower risk cigarettes."<sup>14</sup>

The Surgeon General elaborated that

"Variations in 'tar' to nicotine ratios should be of special concern. It is important to determine the lowest ratios that still produce a satisfying cigarette. Obviously, identical tar and nicotine ratios can occur in cigarettes that have very different standard nicotine yields. Research could show if there is an optimum combination of

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<sup>11</sup> Goldfarb T., Gritz E., Jarvik M.E., et al. Reactions to Cigarettes as a Function of Nicotine and "Tar." Clinical Pharmacology and Therapeutics 19(6): 767-772, 771 (1976).

<sup>12</sup> Id.

<sup>13</sup> Id. at 767.

<sup>14</sup> U.S. Department of Health and Human Services. The Health Consequences of Smoking: The Changing Cigarette, A Report of the Surgeon General. U.S. Gov't Printing Office, 1-252, 58 (1981) (emphasis added).

standard yield and ratio that leads to maximum satisfaction and minimal exposure to toxic products. Cigarettes that vary systematically in tar to nicotine ratios are needed for this research."<sup>15</sup>

It is thus hardly surprising that Philip Morris conducted basic research relating to nicotine, including varying nicotine-to-"tar" ratios, when the Surgeon General, NIH, and many others called for such work. But the even more important point for purposes of this rulemaking is that the unsupported speculation in Dr. Uydess' declaration that this and other nicotine-related research was used to increase the nicotine yields of commercial cigarettes is simply not true. None of this basic research was ever used by Philip Morris to increase nicotine yields in a commercial cigarette. And, for that reason alone, all of this speculation is simply irrelevant to these proceedings.

**B. Philip Morris' Knowledge About  
Tobacco and Agricultural Technology**

Dr. Uydess devotes considerable space in his declaration to Philip Morris' knowledge of, and research on, the tobacco plant. For example, Dr. Uydess reports that Philip Morris maintained information about the "various chemical, mechanical and agronomic properties of the tobaccos it used in its products." Uydess Declaration at 9.

This is true -- but hardly surprising. Like FDA in some of its prior remarks on such agricultural research, Dr. Uydess

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<sup>15</sup> Id. at 184-185 (emphasis added).

ignores the fact that Philip Morris and the other cigarette manufacturers are in the business of selling a processed agricultural product. It would be surprising if the manufacturers did not develop some expertise in the crop from which they make their products. But such expertise and research projects cannot form the basis of FDA jurisdiction.<sup>16</sup>

Contrary to Dr. Uydess' claims, Philip Morris' expertise in, and research on, tobacco is hardly extraordinary. In fact, Philip Morris' research on tobacco plant chemistry and biology over the years has mirrored inquiry and information in the public domain. For decades, the federal government (through both the Department of Agriculture and the National Institutes of Health), state extension services, universities, and other research organizations have all published extensive studies on the chemistry and biology of the tobacco plant.<sup>17</sup> As one USDA

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<sup>16</sup> In Paragraph 16 of his declaration, Dr. Uydess goes so far as to list various analytical equipment owned by Philip Morris and imply that the purpose of this machinery is principally to measure and analyze nicotine. That is preposterous.

The equipment mentioned by Dr. Uydess is standard in chemistry laboratories around the world. Many of those laboratories have gas chromatographic, HPLC, nuclear magnetic resonance, and infrared spectroscopic capabilities. Mass spectrometers are a bit more sophisticated, but they are found in most, if not all, universities that teach graduate students.

None of this equipment is specifically designed for nicotine analyses. Many organic compounds can be, and are, routinely analyzed by such equipment.

<sup>17</sup> To show but a portion of the extensive public literature on this subject, and to debunk Dr. Uydess' claim that Philip Morris was in some unique position because it possessed such knowledge,  
[Footnote continued on next page]

official wrote some 16 years ago:

"The tobacco plant has been the object of extensive basic research and much is known of its genetics, culture, physiology, biochemistry, and post-harvest metabolism."<sup>18</sup>

Indeed, as discussed below, the specific types of research and expertise noted by Dr. Uydess were all the subject of published articles well before Philip Morris conducted its studies.

Finally, and most importantly, Philip Morris' "chemical, biological and engineering" expertise on the basic tobacco plant has never been used to increase artificially the nicotine yield of its commercial cigarettes. Again, for all of its sound and fury, Dr. Uydess' review of this Philip Morris "expertise" proves nothing about the cigarettes the company actually sells (much less the claims it makes for those cigarettes -- the only relevant basis for any assertion of FDA jurisdiction).

### 1. Ratooning

Dr. Uydess' revisionist history is evident in his account of Philip Morris' limited research on the agricultural process

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[Footnote continued from previous page]  
we conducted a simple search of just one well-known database -- Biosis Previews. We have provided in the accompanying Appendices a list of over 200 articles on tobacco biology and chemistry in that one database that were published at, or before, the time Dr. Uydess worked at Philip Morris. A full search of similar publication lists by the various state extension services, public and private universities, and the research community at large would, of course, show many more publications.

<sup>18</sup> Tso T.C. *Modification Through Agricultural Techniques for Developing a Safer Tobacco*. In: Gori G.B., Bock F.G. (eds.) Banbury Report: A Safe Cigarette? 181-190, 188 (1980).

known as "ratooning." In Paragraph 17 of his declaration, Dr. Uydess claims that Philip Morris used "ratooning" to develop "nicotine-enriched" tobacco. That charge is false.

"Ratooning" was not used by Philip Morris with any intent to increase nicotine content in tobacco; the process in fact did not result in "nicotine-enriched" tobacco; and Philip Morris never used this technique (or any other) to grow high-nicotine tobacco for use in any commercial product. Indeed, as Dr. Uydess and FDA so often seem to forget, it is tens of thousands of individual tobacco farmers, not Philip Morris, who grow the tobacco used in Philip Morris cigarettes.

First, as a general matter, ratooning is not used to increase the nicotine content of tobacco, but rather is simply a process that can be employed, under unusual circumstances, to obtain a second crop from many types of plants. As described by one source, "ratooning is the severing of the stem of each tobacco plant at 5-15 cm above ground level, and the fostering of growth of one remaining axillary bud by the removal of others that develop."<sup>19</sup> Thus, a "new" plant is grown from the original root system. The procedure is sometimes used in tropical areas to achieve a second tobacco crop; it may also be used to salvage a

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<sup>19</sup> Whitfield D.M. *Effects of Simulated Hail Damage on Yield and Quality of Flue-Cured Tobacco*. Aust. J. Exp. Agric. Husb. 22:244-248, 244 (1982).

crop that has been cut down prematurely following significant hail damage.<sup>20</sup>

Ratooning is not a viable commercial process for tobacco farmers in most of the tobacco-growing areas of the United States where the overall growing season is not long enough to permit two successive crops. On average, tobacco in the United States takes about three to four months to mature. Yet, the available growing season in the tobacco states is only about four to five months long. To use "ratooning" on a commercial basis, American farmers would therefore need to harvest their first crop of tobacco leaves before the leaves were fully matured -- which would result in a valueless crop.<sup>21</sup> Any suggestion that Philip Morris (or anyone else) could have convinced the tens of thousands of independent tobacco farmers to follow such an uneconomic practice is ludicrous.

Indeed, for the past 30 years, ratooning to obtain two full crops would run afoul of the tobacco support program administered by the United States Department of Agriculture ("USDA"). The USDA closely regulates the production of tobacco and since 1965 has

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<sup>20</sup> As one publication noted 40 years before Dr. Uydess "revealed" ratooning to FDA, after significant hail damage, "[i]t is generally better to grow a sucker from a strong root system than to plow up and plant later." Pointer J.P., Woltz W.G., McCants Co. *When Hail Hits Tobacco*. North Carolina Agricultural Extension Service Circular No. 398, 9 (1956).

<sup>21</sup> As noted in one publication, ratooning tobacco before the first crop's leaves have "ripened sufficiently to be cured" is potentially disastrous: "The fresh leaf therefore has no potential value and crops may have to be abandoned." Whitfield D.M. at 244.

limited the quantity that may be sold. Burley tobacco is controlled by a strict poundage quota, 7 U.S.C. § 1314e, while flue-cured tobacco is controlled by an acreage-poundage quota. 7 U.S.C. § 1314c. The use of ratooning under such weight-based quota systems would make no economic sense because a farmer would need to expend additional labor to harvest two "crops" and yet would still be limited in the amount that he could produce for market.

Second, ratooned tobacco simply does not have higher nicotine content than non-ratooned tobacco. As shown by documents that were reviewed by Dr. Uydess, among others, the very Philip Morris research he notes found that ratooned tobacco was generally lower in total alkaloid content than non-ratooned tobacco.

Philip Morris' ratooning experiments were conducted to determine whether the ratooned tobacco had different characteristics than those of tobacco grown under normal conditions. In addition to examining physical characteristics, routine chemical analyses were conducted on the ratooned tobacco. These analyses measured many constituents -- both "desirable" and "undesirable" -- including, among other things, nitrates, sugars, starch, hot water solubles and alkaloids.<sup>22</sup> The chemical analyses were not conducted for the purpose of determining whether the

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<sup>22</sup> Project 1720 - Tobacco Microstructure "Trends in Greenhouse and Field Tobacco Surface Morphology and Field Tobacco Chemistry" - at 9-10 (Nov. 22, 1982) (distributed to Ian Uydess, among others). (The relevant portion of this and other Philip Morris documents cited herein are provided in the accompanying Appendices.)

ratooned tobacco was "nicotine enriched"; they merely reported nicotine as one of many variables.

Dr. Uydess states that these ratooning experiments "produced tobacco leaves that had higher nicotine levels than the leaves of non-ratooned plants." Uydess Declaration at 15. This is one of the few statements in his declaration which Dr. Uydess does not hedge with a string of qualifiers. It is therefore quite telling that this statement is refuted by the very documents Dr. Uydess received. In fact, the alkaloid levels of the ratooned tobacco were generally lower than those of the non-ratooned "control" tobacco:

	<u>Measured Alkaloids</u> <sup>23</sup>		
	<u>Control</u>	<u>Ratooned #1</u>	<u>Ratooned #2</u>
<u>1979</u>			
Bottom stalk	2.33%	1.27%	1.86%
Middle stalk	3.28%	2.22%	2.54%
Top stalk	4.51%	1.87%	2.68%
<u>1980</u>			
Bottom stalk	2.15%	2.56%	2.64%
Middle stalk	4.47%	3.74%	3.91%
Top stalk	5.33%	3.50%	3.58%

For some stalk positions, the reduction in alkaloids was substantial -- as shown above, in the 1979 study the reductions ranged between 20% and 50%. The only increase in total alkaloids was seen in the bottom stalk position in the 1980 experiment. The overall figures from the two 1980 experiments for all three stalk

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<sup>23</sup> Id.

positions showed a reduction by about 10% and 20%. This is hardly "nicotine-enriched" tobacco.

Finally, Dr. Uydess does not cite any instance of the use of ratooned tobacco -- or any other "nicotine-enriched" tobacco -- in any Philip Morris commercial cigarette. Indeed, he admits that he "do[es] not know if any nicotine-rich leaves that were produced through ratooning ever got into production." Uydess Declaration at 15. Dr. Uydess does not "know" because the fact is that the ratooned tobacco was never used by Philip Morris in commercial production.

As the Industry Comments previously explained, higher-nicotine content tobacco has been rejected by the tobacco companies, including Philip Morris.<sup>24</sup> An article quoted in the Industry Comments provides a few well-known examples:

"During unusually dry seasons, the nitrogen content in U.S. grown tobaccos surges above desirable levels because total nitrogen and alkaloid values, even in normal years, are at the extreme upper end of the range. Buyers are apt to reject the drought-affected crops on a massive scale, as occurred in 1977 with flue-cured and in 1983 with Burley tobacco. Nicotine levels for much of the 1983 Burley Crop were reported to be well above 5 percent. Nearly half of the Burley tobacco grown that year is still stored in stabilization warehouses unsold."<sup>25</sup>

Why, if high-nicotine content tobacco was the "optimal" kind of tobacco, were tobacco farmers unable to sell high-nicotine

<sup>24</sup> Industry Comments at IV-64.

<sup>25</sup> DeJong D.W. *The Role of American Tobacco Leaf Chemistry in Low-Yield Cigarettes: An Agricultural Viewpoint*. *Tabak J. Int'l.* 376-83, 383 (1985) (emphasis added).

tobacco in those dry seasons? The answer is obvious: Philip Morris does not try to purchase -- much less grow -- tobacco specifically for high-nicotine content. And Dr. Uydess has not provided any evidence to the contrary.

## 2. Tissue Culture Research

Dr. Uydess suggests that Philip Morris conducted tissue culture experiments for the purpose of developing and using high-nicotine tobacco. Uydess Declaration at 16. That suggestion is wrong.

First, the fact that Philip Morris conducted tissue culture experiments is neither surprising nor sinister. The use of tissue culture and other forms of biotechnology is widespread throughout the agricultural industry.<sup>26</sup> The type of tissue culture experiments conducted at Philip Morris -- focusing on somaclonal variation -- have been used by others to develop potatoes, corn, oats, rice, barley, tomato, lettuce, sugarcane and wheat, as well as tobacco.<sup>27</sup>

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<sup>26</sup> See, e.g., Evans D.A., Sharp W.R., Medina-Filho H.P. Somaclonal and Gametoclinal Variation. Am. Journal of Botany 71(6):759-774 (1984).

<sup>27</sup> See, e.g., Larkin P.J., Scowcroft W.R. Somaclonal Variation - A Novel Source of Variability from Cell Cultures for Plant Improvement. Theor. Appl. Genet. 60:197-214, 199-205 (1981).

Evans D.A., et al. at 761-763.

Larkin P.J., Brettell R.I.S., Ryan S.A., et al. Somaclonal Variation: Impact on Plant Biology and Breeding Strategies. In: Zailten M., Day P., Hollaender A. (eds.) Biotechnology in Plant  
[Footnote continued on next page]

Somaclonal variation refers to natural genetic variations occurring among cultured -- or "cloned" -- plant cells taken from a single plant or species.<sup>28</sup> Agricultural researchers discovered that tissue cultures derived from such plant cells can reflect genetic variability.<sup>29</sup> It was soon determined that individual cells with a specific characteristic could be "cloned" to generate plants ("somaclones") that should (at least theoretically) "express" the same characteristic.<sup>30</sup> This process was well-known long before Philip Morris began conducting its research. As stated in one article, the "phenomenon of somaclonal variation has

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Science -- Relevance to Agriculture in the Eighties 83-100, 92 (1987).

<sup>28</sup> See, e.g., Evans D.A., et al. at 760.

<sup>29</sup> Larkin P.J., Scowcroft W.R. *Somaclonal Variation - A Novel Source of Variability from Cell Cultures for Plant Improvement*. Theor. Appl. Genet. 60:197-214, 197 (1981).

<sup>30</sup> See Evans D.A., et al. at 759.

The process of "cloning" new plants from individual cells is as follows: A small portion of a plant (the "explant") is placed into a test tube or petri dish that is then filled with a nutrient-containing medium to encourage cell growth. As the culture is incubated, the cells from the explant proliferate and form a mass of tissue, the callus. The callus doubles in size over a period of a few weeks. The callus is then placed on fresh medium and within 90 days forms a "plantlet". Plantlets, which are approximately 3 to 4 cm in height, are then removed from the culture and planted in soil where they will grow into mature plants. See Hutchins E.M. *Micropropagation of Tobacco*. Carolina Tips 47(9):33-35 (1984).

been well documented from various perspectives in a number of reviews."<sup>31</sup>

Specifically, the use of tobacco in tissue culture experiments was widely reported in the public literature well before Philip Morris began its research in that area.<sup>32</sup> As one 1984 article noted:

"Pioneering scientists in the field of plant tissue culture used . . . tobacco plants in their experiments. Tobacco was a favorite research material because it was easily cultured. . . . Tobacco is used as a model reference material in plant tissue culture experiments and will probably continue in this role in the future."<sup>33</sup>

Nor is Dr. Uydess' statement that Philip Morris developed nicotine in the tissue cultures evidence of some secret process.

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<sup>31</sup> Larkin P.J., Brettell R.I.S., Ryan S.A., et al. at 83 (citing, among others, Skirvin (1978), Chaleff (1981)).

<sup>32</sup> See, e.g., Murashige T., Skoog F. A Revised Medium for Rapid Growth and Bio Assays with Tobacco Tissue Cultures. *Physiol. Plant.* 15:473-497 (1962).

Gibbs J.L., Dougall D.K. The Growth of Single Cells from Nicotiana Tabacum Callus Tissue in Nutrient Medium Containing Agar. *Exp. Cell Res.* 40:85-95 (1965).

Laetsch W.M., Stetler D.A. Chloroplast Structure and Function in Cultured Tobacco Tissue. *American Journal of Botany*, 52: 798-804 (1965).

Linsmaier E.M., Skoog F. Organic Growth Factor Requirements of Tobacco Tissue Cultures. *Phys. Plantarum* 18:100-127 (1965).

Witham F.H. Effect of 2,4-Dichlorophenoxyacetic Acid on the Cytokinin Requirement of Soybean Cotyledon and Tobacco Stem Pith Callus Tissues. *Plant Physiol.* 43:1455-1457 (1968).

<sup>33</sup> Hutchins E.M., Micropropagation of Tobacco. *Carolina Tips* 47(9):33-35 (Sept. 1, 1984).

Alkaloids, such as nicotine, had been the subject of tissue culture studies published years before Philip Morris' work in the area.<sup>34</sup> Many of these earlier studies involved production of nicotine in tobacco cell cultures.<sup>35</sup> One article published 33 years ago stated, "It has long been known that tobacco root

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<sup>34</sup> As early as 1969, researchers noted that "cell cultures derived from plants which synthesize particular secondary metabolites, such as alkaloids and steroids, have, in many instances, been shown to synthesize these same compounds." Veliky I., Sandkvist A., Martin S.M. *Physiology of, and Enzyme Production by, Plant Cell Cultures. Biotechnology and Bioengineering IX:1247-1254, 1248 (1969) (emphasis added).*

Many researchers subsequently investigated the generation of alkaloids in tissue culture:

Mulder-Krieger T., Verpoorte R., deGraaf Y.P., et al. *The Effects of Plant Growth Regulators and Culture Conditions on the Growth and Alkaloid Content of Callus Cultures on Cinchona Pubescens.* *Planta Med.* 46:15-18 (1982).

Koblitz H., Koblitz D., Schmauder H.P., Gröger D. *Studies on Tissue Cultures of the Genus Cinchona L. Alkaloid Production in Cell Suspension Cultures.* *Plant Cell Reports* 2:122-125 (1983).

<sup>35</sup> Furuya T., Kojima H., Syono K. *Regulation of Nicotine Biosynthesis by Auxins in Tobacco Callus Tissues.* *Phytochem.* 10:1529-1532 (1971).

Tabata M., Yamamoto H., Hiraoka, et al. *Regulation of Nicotine Production in Tobacco Tissue Culture by Plant Growth Regulators.* *Phytochem.* 10:723-729 (1971).

Takahashi M., Yamada Y. *Regulation of Nicotine Production by Auxins in Tobacco Cultured Cells in Vitro.* *Agr. Biol Chem.* 37(7):1755-1757 (1973).

Tabata M., Hiraoka N. *Variation of Alkaloid Production in Nicotiana Rustica Callus Cultures.* *Physiol. Plant.* 38:19-23 (1976).

Ogino T., Hiraoka N., Tabata M. *Selection of High Nicotine-Producing Cell Lines of Tobacco Callus by Single-Cell Cloning.* *Phytochem.* 17:1907-1910 (1978).

cultures can biosynthesize the alkaloids nicotine and anabasine."<sup>36</sup> Indeed, even the National Institutes of Health funded studies involving the somaclonal variation of nicotine in tissue cultures.<sup>37</sup>

Second, and more importantly, the goal of Philip Morris' tissue culture work was not the maximization of nicotine in tobacco plants. Early tissue culture research investigated the development in vitro of tobacco cells that had both high and low levels of nicotine. But, as Dr. Uydess should recall, this initial work was done solely to determine whether the process of somaclonal variation seen in cells was expressed in plants regenerated from those cells. It never led to the development of a high-nicotine content tobacco for commercial purposes. To the contrary, one goal of the nicotine-related tissue culture project was to develop a reduced nicotine plant.

Dr. Uydess misleadingly states that "[a] variety of cultural techniques (including variations in growth conditions, nutrients, plant hormones, etc.)" were used to "maximize" the production of "targeted materials," which he defines as nicotine.

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<sup>36</sup> Staba E.J. *The Biosynthetic Potential of Plant Tissue Cultures*. *Developments in Industrial Microbiology* 4:193-198, 193 (1963).

<sup>37</sup> Kinnersley A.M., Dougall D.K. *Correlation Between the Nicotine Content of Tobacco Plants and Callus Cultures*. *Planta* 149:205-206, 206 (1980) (thanking NIH "for supporting this work through Grant No. GM 25994").

Kinnersley A.M., Dougall D.K. *Variation in Nicotine Content of Tobacco Callus Cultures*. *Planta* 154:447-453, 452 (1982) (thanking NIH "for supporting this work through Grant No. GM 25994").

Uydess Declaration at 16. What Dr. Uydess is presumably referencing are the attempts to "grow" cells that expressed nicotine in measurable amounts in cultures. As reported in the published scientific literature, nicotine, like other secondary metabolites, is not readily produced by tobacco cells in vitro.<sup>38</sup> To measure any variation or difference among the cells' nicotine production -- whether to develop a somaclone which is more or less efficient at expressing nicotine -- it is necessary that the cells generate measurable amounts of nicotine in vitro. Philip Morris researchers therefore used a variety of cultural techniques -- such as the use of hormones and nutrients -- to encourage (or, as Dr. Uydess puts it, "maximize") the production of nicotine in vitro. But those techniques were nothing more than standard procedures to encourage cell growth in cultures.<sup>39</sup>

Dr. Uydess' suggestion that the "overall goal" of the tissue cultures was the "optimization" of nicotine in tobacco plants is wrong. In fact, just the opposite was true. As the

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<sup>38</sup> See Lockwood G.B., Essa A.K. *The Effect of Varying Hormonal and Precursor Supplementations on Levels of Nicotine and Related Alkaloids in Cell Cultures of Nicotiana Tabacum*. Plant Cell Reports 3:109-111, 109 (1984).

Pinol M.T., Palazon J., Serrano M. *Growth and Nicotine Content of Tobacco Callus Cultures Without Organogenesis*. Plant Science Letters 35:219-223 (1984).

<sup>39</sup> Hutchins E.M. *Micropropagation of Tobacco, Carolina Tips* 47(9):34 (Sept. 1, 1984) (recommending the use of "macronutrients" and "hormones" to encourage the growth of tobacco cells in vitro).

final report on this project states, the goal was to produce tobacco with reduced levels of nicotine:

"The goal of producing a burley tobacco plant with reduced green leaf nicotine levels was pursued through the techniques of somaclonal variation.

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"Reducing the nicotine level in green tobacco leaf has been a continuing challenge. Other than classical breeding techniques, which are very time consuming, or chemical manipulation of the cured leaf, no method is known which might accomplish this goal. The plant tissue culture laboratory took on this challenge with the goal of producing a burley (Kentucky 10) tobacco plant with reduced green leaf nicotine levels and acceptable subjectives through somaclonal variation."<sup>40</sup>

Dr. Uydess' description of the related work conducted for Philip Morris on a contract basis by Crop Genetics International is equally misleading on this fundamental point. Dr. Uydess correctly states that Crop Genetics entered into a joint venture with Philip Morris "to explore the application of plant tissue culture and cloning techniques to the selection/regeneration of tobacco plants with 'most desirable' characteristics (characteristics selected/targeted by Philip Morris)." Uydess Declaration at 16. But Dr. Uydess does not identify the specific characteristics that were "targeted" by Philip Morris. To be sure, he implies that Philip Morris was looking to maximize nicotine content; but even he does not say that per se.

<sup>40</sup> Report Project 1730 - Plant Tissue Research (Jan. 9, 1987) (emphasis added).

The truth is that while Philip Morris identified a number of desirable characteristics that it hoped Crop Genetics could develop in tobacco plants through somaclonal variation, none of those characteristics was high-nicotine content. Indeed, at one point, Philip Morris suggested that one desirable characteristic that might be pursued by Crop Genetics was a "low-alkaloid" tobacco plant.<sup>41</sup>

Last, but by no means least, even Dr. Uydess again admits that "[w]hile Philip Morris explored the potential (future) use of this and related technologies, they did not at that time employ it in the manufacture of any of their products." Uydess Declaration at 16 (emphasis added). In fact, Philip Morris has never used biotechnology to increase the nicotine levels in tobacco plants that were then used in commercial cigarettes. Once again, this basic research is thus entirely irrelevant to any assertion of FDA jurisdiction.

**C. Research On Nicotine Analogs And  
The Research of Dr. DeNoble**

In Paragraphs 19 and 20 of his declaration, Dr. Uydess alludes to Philip Morris research projects in which he was not involved to try to suggest that the company had concluded that nicotine is "addictive." Uydess Declaration at 16-17. In fact,

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<sup>41</sup> Letter from W. Farone to Crop Genetics International, attaching list of projects of interest to Philip Morris (July 18, 1983).

neither the analog program nor the behavioral research program cited by Dr. Uydess demonstrates that nicotine is addictive.

Dr. Uydess' second-hand speculations about these projects are contradicted by the facts, as shown by both the contemporaneous reports of the researchers who actually were involved and their subsequent testimony on that research. For FDA to give any weight to these speculations of Dr. Uydess -- especially when the facts of both research programs have already been detailed in Philip Morris' prior comments -- would be arbitrary and capricious.

#### 1. Nicotine Analog Program

The analog program is irrelevant to the current FDA proceedings. As explained in detail in Philip Morris' individual comments,<sup>42</sup> this limited research never resulted in anything close to a commercial product. Moreover, many well-respected researchers outside the tobacco industry were also engaged in research on nicotine analogs before Philip Morris ever conducted such theoretical research.<sup>43</sup> The fact that Philip Morris

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<sup>42</sup> Comments of Philip Morris Incorporated ("PM Comments") at 23-29 (Jan. 2, 1996).

<sup>43</sup> See, e.g., Barlow R.B., Dobson N.A. *Nicotine Monomethiodide*. J. Pharm. Pharmacol. 7: 27-34 (1954).

Cushman M., Castagnoli N. Jr. *The Synthesis of trans-3'-Methylnicotine*. J. Org. Chem. 37(8): 1268-1271 (1972).

Erdtman H., Haglid F., Wellings I. *Synthetic Analogues of Nicotine*. I. Acta Chem. Scand. 17(6): 1717-1726 (1963).

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similarly conducted research on analogs thus provides no evidence of the "intended use" of any commercial cigarettes marketed by Philip Morris (none of which, it bears repeating, contained any such analog).

This analog research likewise was not, as Dr. Uydess claims, premised on the "habituating effect" of nicotine. Uydess

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Haglid F. *Studies on Pyridine Alkaloids and Their Analogues*. Acta Pharm. Suecica 4: 117-138 (1967).

Larson P.S., Haag H.B., Silvette H., Tobacco: Experimental and Clinical Studies, App. II, "Some Notes on the Pharmacology of Certain Derivatives of Nicotine," (1961) at 800-11.

Leete E. *Alkaloid Biosynthesis*. In: Nord F.F. (ed.) Advances in Enzymology and Related Areas of Molecular Biology 32: 373-422 (1969).

Nandi B.K. *Synthesis of Benzonictine*. J. Indian Chem. Soc. 17: 285-288 (1940).

Rueppel M.L., Rapoport H. *Aberrant Alkaloid Biosynthesis. Formation of Nicotine Analogs from Unnatural Precursors in Nicotiana Glutinosa*. J. Amer. Chemical Soc. 93(25): 7021-7028 (1971).

Tschitschiban A.E., Kirssanow A.W. *Aminierung des Nicotins mit Natrium-und Kaliumamid*. Ber. 57: 1163-1168 (1924).

Waterman L., Oosterhus A.G. *On the Pharmacological Properties of dl Alfa-Nicotine*. J. Pharmacol. & Exptl. Therapeutics 63: 318-29 (1938).

Yamamoto I., Soeda Y., Kamimura H., et al. *Studies on Nicotinoids as an Insecticide, Part VII. Cholinesterase Inhibition by Nicotinoids and Pyridylalkylamines -- Its Significance to Mode of Action*. Agr. Biol. Chem. 32(11): 1341-1348 (1968).

A more complete list of such research may be found in Philip Morris' prior comments on this topic. See PM Comments at 24-29 n. 69-70.

Declaration at 17. Rather, the research involved the synthesis and characterization of compounds having a structure similar to nicotine and an evaluation of their chemical and physical properties. The research had a number of objectives, one of which was to respond to concerns expressed by some in the public health community about the peripheral nervous system effects (*i.e.*, blood pressure effects) associated with nicotine.

To screen selectively for the cardiovascular effects of nicotine using analogs, it was necessary to develop a behavioral, peripheral and central nervous system profile of nicotine. Researchers at Philip Morris, together with scientists at outside universities, evaluated both natural nicotine and the analogs using a variety of standard in vivo and in vitro tests.

Despite years of experimentation, Philip Morris never developed a commercially useful analog. The theoretical nature of the project -- and the fact that it was hardly some commercial secret to be guarded at all cost -- is demonstrated by the fact that findings from the Philip Morris program were contemporaneously published in the scientific and patent literature by Philip Morris researchers and others.<sup>44</sup> Every one

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<sup>44</sup> See, *e.g.*, Chavdarian C.G. *Optically Active Nicotine Analogues. Synthesis of (S)-(-)-2,5-Dihydro-1-methyl-2-(3-pyridyl)pyrrole ((S)-(-)-3',4'-Dehydronicotine)*. J. Org. Chem. 48(9): 1529-1531 (1983).

Chavdarian C.G., Sanders E.B., Bassfield R.L. *Synthesis of Optically Active Nicotinoids*. J. Org. Chem. 47(6): 1069-1073 (1982).

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of these publications and patent applications was made either before, or while, Dr. Uydess was at the company. Perhaps, because he was not part of the program, he was not aware of them. But

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Chavdarian C.G., Seeman J.I., Wooten J.B. *Bridged Nicotines. Synthesis of cis-2,3,3a,4,5,9b-Hexahydro-1-methyl-1H-pyrrolo[2,3-f]quinoline.* J. Org. Chem. 48(4): 492-494 (1983).

Comes R.A., Core M.T., Edmonds M.D., et al. *The Preparation of Carbon-14 Labelled Tobacco Constituents, II, The Synthesis of D1-Nicotine (2'-<sup>14</sup>C).* J. Labelled Compounds IX(2): 253-259 (1973).

Cox R.H., Kao J., Secor H., et al. *Assessment of Isolated Electronic Effects on Conformation. NMR Analysis of Nicotine and Related Compounds and Ab Initio Studies of Model Compounds.* Elsevier Sci. Publishers B.V. 93-106 (1985).

Edwards W.B. III, Glenn D.F., Green F., et al. *The Preparation of Tobacco Constituents Incorporating Stable Isotopes, I. The Synthesis of d, l-Nornicotine-1'-<sup>15</sup>N and d, l-Nicotine-1'-<sup>15</sup>N.* J. Labelled Compounds XIV(2): 255-261 (1978).

Edwards W.B. III, McCuen R. *Preparation of Optically Pure (R)-(+)-Nicotine. Studies on the Microbial Degradation of Nicotinoids.* J. Org. Chem. 48(15): 2484-2487 (1983).

Sanders E.B., DeBardleben J.F., Osdene T.S. *Nicotine Chemistry. 5'-Cyanonicotine.* J. Org. Chem. 40(19): 2848-2849 (1975).

Sanders E.B., Secor H.V., Seeman J.I. *Synthesis of 2,3-Disubstituted Pyridines Ortho-Formylation and Ortho-Acylation of 2-Alkylpyridines.* J. Org. Chem. 41(15): 2658-2659 (1976).

Secor H.V., Chavdarian C.G., Seeman J.I. *The Radical and Organometallic Methylation of Nicotine and Nicotine N-Oxide.* Tetrahedron Lett. 22(33): 3151-3154 (1981).

Secor H.V., Edwards W.B. III. *Nicotine Analogues: Synthesis of Pyridylazetidines.* J. Org. Chem. 44(18): 3136-3140 (1979).

Secor H.V., Seeman J.I. *The Preparation of "Elongated" Nicotine Analogues.* Heterocycles 24(6): 1687-1698 (1986).

Seeman J.I., Chavdarian C.G., Kornfeld R.A., et al. *Nicotine*  
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that is no excuse for any suggestion that Philip Morris "hid" this basic, non-commercial research. Uydess Declaration at 20-22. Indeed, Philip Morris even made the compounds available to a

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Chemistry: The Addition of Organolithium Reagents to (-)-Nicotine. Tetrahedron 41(3): 595-602 (1985).

Seeman J.I., Chavdarian C.G., Secor H.V. Synthesis of the Enantiomers of Nornicotine. J. Org. Chem. 50(25): 5419-5421 (1985).

Seeman J.I., Chavdarian C.G., Secor H.V., et al. Preparation of Hydroxyalkyl-Substituted Nicotinoids. J. Org. Chem. 51(9): 1548-1551 (1986).

Seeman J.I., Clawson L.E., Secor H.V. Nicotine Chemistry. The Addition of Alkyl Radicals to (S)-(-)-Nicotine: Synthesis of Optically Active 6-Alkylnicotines. Synthesis 10: 953-955 (1985).

Seeman J.I., Secor H.V., Forrest G. Convenient Synthesis of N-CD<sub>3</sub> Labelled Nicotine and Nicotine Analogues. J. Labelled Compounds and Radiopharmaceuticals XVI(3): 387-395 (1978).

Seeman J.I., Secor H.V., Hartung H., et al. Steric Effects in Conformationally Mobile Systems. The Iodomethylation of 1-Methyl-2-arylpyrrolidines Related to Nicotine. J. Amer. Chemical Soc. 102(26): 7741-7747 (1980).

Seeman J.I., Secor H.V., Howe C.R., et al. Organometallic Methylation of Nicotine and Nicotine N-Oxide. Reaction Pathways and Racemization Mechanisms. J. Org. Chem. 48(25): 4899-4904 (1983).

Whidby J.F., Edwards W.B. III, Pitner T.P. Isomeric Nicotines. Their Solution Conformation and Proton, Deuterium, Carbon-13, and Nitrogen-15 Nuclear Magnetic Resonance. J. Org. Chem. 44(5): 794-798 (1979).

See also U.S. Patent, No. 4,220,781, Process for Preparing 2-Alkyl Nicotinoids, (Philip Morris, Inc.), Sept. 2, 1980.

U.S. Patent, No. 4,155,909, 2-Alkyl Nicotinoids and Processes For Their Production, (Philip Morris, Inc.), May 22, 1979.

This is only a partial list of the publications and patent applications detailing the findings of the Philip Morris analog

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number of researchers outside Philip Morris, including researchers at universities and at FDA.<sup>45</sup> Perhaps Dr. Uydess believes all of these outside groups were also part of some grand conspiracy.

In short, there is simply no merit in Dr. Uydess' suggestions that this basic analog research was somehow inappropriate or had any bearing on the commercial "intentions" of Philip Morris.

## **2. Dr. DeNoble's Research On Nicotine As A "Reinforcer"**

Dr. Uydess' suggestion that the research that Dr. DeNoble conducted on nicotine as a "reinforcer" in rats proved that nicotine is "addictive" is contradicted both by Dr. DeNoble's contemporaneous reports while at Philip Morris and by his subsequent testimony under oath. Far from being silent about the use of the term "addiction" during his work at Philip Morris, as Dr. Uydess tries to suggest (Uydess Declaration at 17), Dr. DeNoble repeatedly advised his colleagues that he believed

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research. A more complete list may be found in Philip Morris' prior Individual Comments filed on January 2, 1996. See PM Comments at 26-29, n.70.

<sup>45</sup> Throughout the 1970s and 1980s, a variety of outside researchers were engaged in research on nicotine analogs. Philip Morris provided a number of those researchers, including some with the federal government, with analogs for their own purposes. They included researchers at the University of California at San Francisco (1970), Stanford University (1977), Tufts University (1980), University of Kentucky (1981), University of Illinois (1985), University of Missouri (1986), and Case Western Reserve (1993). Indeed, analogs were sent to scientists working at FDA (1985) and the National Institutes of Health (1987 and 1994).

smoking and nicotine were not "addictive." Even four years after leaving Philip Morris, and again in his congressional appearance in 1994, Dr. DeNoble testified under oath that his research on reinforcement had not shown that nicotine was "addictive."

As explained in greater detail in Philip Morris' individual comments, Dr. DeNoble researched the self-administration of nicotine in rats.<sup>46</sup> Such self-administration studies are one procedure to identify reinforcing effects of a compound. But, as Dr. DeNoble himself recognized, the fact that an animal may self-administer a substance does not prove that the substance is reinforcing in humans -- much less that it is "addictive."<sup>47</sup>

Far from being some deep, dark secret, self-administration research on nicotine was published well before Dr. DeNoble was employed at Philip Morris; and by the time Dr. DeNoble began conducting his studies at Philip Morris in 1980, research scientists outside the industry had already reported on the reinforcing effects of nicotine.<sup>48</sup>

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<sup>46</sup> PM Comments at 30-34.

<sup>47</sup> The general issue of animal self-administration studies is also discussed in the Industry Comments. See Industry Comments at III-30 to III-37.

<sup>48</sup> For example, the Surgeon General's 1979 Report notes that a 1977 article by R.M. Stephens found that nicotine facilitates reinforced behavior in rats. See U.S. Dept. of Health, Education, and Welfare, Smoking and Health, Pub. No. DHEW (PHS) 79-50066, A Report of the Surgeon General 16-12 (U.S. Government Printing Office 1979). See also Stephens R.M. *Psychophysiological Variables in Cigarette Smoking and Reinforcing Effects of Nicotine*. Addictive Behavior 2: 1-7 (1977).

As early as 1977, Lang, et al. had published studies reporting that rats would self-administer nicotine.<sup>49</sup> Indeed, the Surgeon General's Report in 1988 stated that it had been "shown conclusively" as early as 1981 that nicotine was an "efficacious positive reinforcer for animals."<sup>50</sup>

Dr. DeNoble's own research on nicotine reinforcement largely replicated the research of Dr. Lang on the self-administration of nicotine in rats. In the course of that research, Dr. DeNoble found that the rats would intravenously self-administer nicotine, but the overall rates of responding were low relative to other reinforcers.<sup>51</sup> As he put it, "nicotine can function as a positive reinforcer for rats, and that the

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<sup>49</sup> See Lang W.J., Latiff A.A., McQueen A., et al. *Self-Administration of Nicotine With and Without a Food Delivery Schedule*. Pharmacology, Biochemistry & Behavior 7: 65-70 (1977).

See also Lang W.J. *Factors Influencing the Self-Administration of Nicotine and Other Drugs By Rats*, 11/22 Proceedings of the Australian Physiological & Pharmacology Society, 33-36 (1980).

<sup>50</sup> U.S. Dept. of Health and Human Services, Pub. No. DHHS (CDC) 88-8406, The Health Consequences of Smoking: Nicotine Addiction. A Report of the Surgeon General 181 (U.S. Government Printing Office 1988) ("Surgeon General's 1988 Report"). A summary table of nicotine self-administration research that was included in the Surgeon General's 1988 Report indicates that studies on this topic began in the late 1960s and 1970s, and numerous studies were conducted in the early 1980s. Id. at 183-88.

<sup>51</sup> DeNoble V.J., Mele P.C., Ryan F.J., Nicotine as a Positive Reinforcer for Rats: Effects of Infusion Dose and Fixed Ratio Size 4 (unpublished manuscript) (emphasis added) ("Reinforcement Manuscript").

reinforcing effect is relatively weak compared to other intravenously delivered reinforcers."<sup>52</sup>

Dr. DeNoble's research at Philip Morris thus did not establish that smoking is "addictive." To the contrary, his research found that nicotine, when administered intravenously to laboratory animals, is only a "weak reinforcing agent" -- in the class of nonaddictive chemical compounds, such as saccharin and water.<sup>53</sup>

Moreover, as Dr. DeNoble himself explained, the fact that a substance is a positive reinforcer does not mean that the substance is "addictive." During his work at Philip Morris, Dr. DeNoble advised his colleagues that self-administration cannot be equated with "addiction."<sup>54</sup> For example, an internal memorandum from Dr. DeNoble stated that "self-administration techniques establish the reinforcing properties of a stimulus event not its 'addiction potential.'"<sup>55</sup> Another memorandum from Dr. DeNoble noted the "[m]anifest absurdity" and "the dangers of

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<sup>52</sup> Memorandum to Seligman from DeNoble, Dunn, Osdene and Ryan, "Self-Administration - Reinforcement - 'Addiction'" (July 23, 1980) ("July 23, 1980 Memorandum").

<sup>53</sup> See, e.g., id.; Reinforcement Manuscript at 4.

<sup>54</sup> See, e.g., Memorandum to Osdene from DeNoble, "Article 'The Nicotine Fix,'" (September 29, 1980) and accompanying attachments ("September 29, 1980 Memorandum").

<sup>55</sup> Memorandum to Osdene from DeNoble, "Critique of National Institute on Drug Abuse Technical Review on Cigarette Smoking as an Addiction," (October 22, 1980) ("October 22, 1980 Memorandum").

using self-administration as the criteria for 'addiction.'"<sup>56</sup> In yet another memorandum, Dr. DeNoble explicitly refuted efforts by anti-smoking groups to equate reinforcement with "addiction" and noted that "[s]cientists all over the world have shown that the reinforcing properties of a compound do not indicate that the compound is 'addictive.'"<sup>57</sup>

Not only did Dr. DeNoble's research not find "addiction," it also affirmatively demonstrated that nicotine does not produce the physiological effects that he and other scientists recognized as hallmarks of "addictive" substances, such as physical dependence<sup>58</sup> and withdrawal.<sup>59</sup>

Dr. DeNoble's views during his time at Philip Morris, as conveyed contemporaneously in writing to his colleagues at the company, likewise directly contradict Dr. Uydess' characterization

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<sup>56</sup> September 29, 1980 Memorandum.

<sup>57</sup> Memorandum to Osdene from DeNoble and Dunn, "Article 'The Nicotine Fix,'" (July 28, 1980) ("July 28, 1980 Memorandum").

<sup>58</sup> As Dr. DeNoble explained in one of his reports: "[W]ork within our own laboratory [at Philip Morris] suggests that nicotine self-administration does not fit the accepted criteria for drug dependence, and falls into a class of more conventional self-administered reinforcers, (e.g., food, saccharin, etc.) that do not produce physical dependence." October 22, 1980 Memorandum (emphasis added).

Dr. DeNoble's study of reinforcement likewise concluded that "termination of prolonged access to nicotine under conditions in which it functions as a positive reinforcer does not result in physiological dependence." Reinforcement Manuscript, in Abstract. :

<sup>59</sup> See Oversight Hearing on Tobacco Products: Hearings Before the Subcomm. on Health and the Environment of the House Comm. on Energy and Commerce, 103d Congress, 2d Sess. 28-31 (April 28, 1994) (testimony of Victor J. DeNoble).

of that work (apparently based on his recollection of casual conversations more than a decade ago) as "evidence" that smoking is "addictive." In documents written at the time of his research, Dr. DeNoble repeatedly stated that nicotine is not "addictive" and cannot be viewed as a "drug."<sup>60</sup>

In 1988 -- four years after he had left Philip Morris -- Dr. DeNoble reiterated in sworn testimony that his research had not shown that nicotine was "addictive."<sup>61</sup> Dr. DeNoble testified that his experiments at Philip Morris never changed his opinion that nicotine was merely a "reinforcer" in the class of such nonaddictive substances as saccharin and water.<sup>62</sup> When pressed further on his views about nicotine and "addiction", he replied:

"I don't believe that it is a correct statement to say that nicotine is addicting. I don't believe that; no."<sup>63</sup>

Indeed, even in April 1994, in testimony before a House Subcommittee, Dr. DeNoble agreed that his reinforcement research did not demonstrate that nicotine is "addictive." He likewise acknowledged that he had told his colleagues at Philip Morris that

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<sup>60</sup> See, e.g., July 23, 1980 Memorandum; July 28, 1980 Memorandum; September 29, 1980 Memorandum.

<sup>61</sup> Deposition of Victor DeNoble, Shires v. Celotex Corp., No. 85-7141 (E.D. Pa.).

<sup>62</sup> Id. at 103.

<sup>63</sup> Id. at 173-174.

his research with rats indicated that nicotine was a "reinforcing agent" and that "[i]t's not addiction."<sup>64</sup>

These statements by Dr. DeNoble under oath make it clear that his reinforcement studies did not establish that nicotine is "addictive." Dr. DeNoble's own contemporaneous memoranda and subsequent sworn testimony thus undercut Dr. Uydess' unsubstantiated speculations. By his own testimony, Dr. DeNoble's research on self-administration provides no evidence to support Dr. Uydess' allegation that cigarette manufacturers intend their products to result in "addiction."

#### D. Dr. Gullotta's Research

Dr. Uydess' statements concerning the electrophysiological research conducted by Dr. Frank Gullotta are filled with innuendo and suggestion. But it is unclear -- given Dr. Uydess' repeated use of hedge words such as "possibly," "presumably," and "it is my understanding" -- what he is really saying about Dr. Gullotta's work, or whether he is saying anything of substance at all. Uydess Declaration at 18-20. In any event, neither Dr. Uydess' speculations regarding Dr. Gullotta's work, nor the work itself, provides any basis for FDA's assertion of jurisdiction over cigarettes.

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<sup>64</sup> Oversight Hearing on Tobacco Products: Hearings Before the Subcomm. on Health and the Env't of the House Comm. on Energy and Commerce, 103d Cong., 2d Sess. 54 (Apr. 28, 1994) (testimony of Victor J. DeNoble).

Dr. Gullotta was hired to conduct basic research in response to published work on the EEG effects of smoking. Contrary to Dr. Uydess' claims (Uydess Declaration at 18), Dr. Gullotta's EEG work was not designed to, and did not, "help formulate new products." It was not designed to, and did not, seek to determine whether nicotine or cigarette smoking is "addictive." Id. And it most certainly was not designed to, and did not, determine whether nicotine (or any other component of cigarette smoke) is similar to cocaine. Id. at 20.

In fact, Dr. Uydess' declaration reveals precious little understanding of Dr. Gullotta's work. Dr. Uydess concedes that the sole basis for his comments on Dr. Gullotta's work was a series of conversations, "usually over coffee at informal, early morning meetings in his [Dr. Gullotta's] office." Uydess Declaration at 7.

Similarly, Dr. Uydess' training did not equip him to understand even these informal descriptions of Dr. Gullotta's work. Dr. Uydess' post-graduate training is in cell biology and microbiology; Dr. Gullotta's Ph.D. is in experimental psychology, a totally unrelated field. Moreover, Dr. Uydess had no practical experience at Philip Morris that would entitle him to comment on Dr. Gullotta's research. Dr. Uydess never participated in, or was even present at, an experiment conducted by Dr. Gullotta or his colleagues. Dr. Uydess had nothing to do with the design of the experiments. And Dr. Uydess was not part of Dr. Gullotta's reporting line.

Dr. Uydess' lack of knowledge about Dr. Gullotta's research is quite evident from his statements suggesting that that work was somehow unique. Uydess Declaration at 20. Contrary to Dr. Uydess' suggestion that Dr. Gullotta's EEG studies involved techniques never previously used to study the effects of cigarettes or their constituents, various effects of smoking on EEG patterns had been reported as early as 1958.<sup>65</sup> The 1964 Surgeon General's Report likewise took note of the developing literature on EEG studies of smoking.<sup>66</sup> Additional work soon followed.<sup>67</sup> Not surprisingly, this extensive published work on

<sup>65</sup> See Hauser H., et al. Electroencephalographic Changes Related to Smoking. Electroencephalography and Clin. Neurophysiology 10:576 (1958).

<sup>66</sup> U.S. Dept. of Health, Education and Welfare, Pub. No. 1103, Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service 70 (U.S. Government Printing Office 1964) ("Surgeon General's 1964 Report").

<sup>67</sup> See, e.g., Domino E.F. Electroencephalographic and Behavioral Arousal Effects of Small Doses of Nicotine: A Neuropsychopharmacological Study. In: Murphree H.B. (ed.) The Effects of Nicotine and Smoking on the Central Nervous System, Ann. N.Y. Acad. of Sci. 142:216-244 (1967).

Murphree H.B. Electroencephalographic Effects of Caffeine, Nicotine, Tobacco Smoking, and Alcohol. In: Itil T.M. (ed.) Psychotropic Drugs and the Human EEG. Modern Problems of Pharmacopsychiatry 8:22-36 (1974).

Knott V.J., Venables P.H. EEG Alpha Correlates of Non-Smokers, Smoking, and Smoking Deprivation. Psychophysiology 14:150-56 (March 1977).

Indeed, in October 1978, an entire International Symposium entitled The Electrophysiological Effects of Nicotine was held in France; its proceedings were subsequently published in 1979. See Proceedings of the International Symposium on the Electrophysiological Effects of Nicotine, Paris, France, October 1978 19-20 (1979).

smoking and EEG patterns was discussed at conferences attended by Philip Morris researchers in the 1970s. It was in this context of increasing interest in the EEG study of cigarette smoking that Philip Morris added Dr. Gullotta to its Research Department in June 1977.

Dr. Uydess appears to believe that Dr. Gullotta's work, particularly his use of an "olfactometer", was "pioneering" research into the pharmacological effects of nicotine. Uydess Declaration at 20.<sup>68</sup> In fact, Dr. Gullotta's "olfactometer" work involved EEG-assisted investigations into flavor issues, not nicotine pharmacology. None of that "olfactometer" work involved nicotine at all.

As described in greater detail in the Industry Comments,<sup>69</sup> flavor is an important component of a cigarette smoker's pleasure or satisfaction; and that overall flavor is affected by at least three sensory aspects of the smoke: taste, smell, and trigeminal

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<sup>68</sup> "Dr. Gullotta's pioneering work in this area appeared to demonstrated [sic] that a cause-and-effect relationship could be measured in the central nervous system between exposure to nicotine and changes in the electrochemical activity of the human brain." Uydess Declaration at 20.

To be sure, Dr. Gullotta's work reported an EEG effect of nicotine. But EEG-observed "changes in the electrochemical activity of the human brain" as a result of smoking had been widely discussed in the literature for 20 years, and a finding similar to Dr. Gullotta's had been reported in Remond A., et al. *The Action of Smoking on Visual Evoked Potentials, Biofeedback, EEG Changes and Autonomous Responses* In: Redmond A., Izard, C. (eds.) Electrophysiological Effects of Nicotine: Proceedings of the International Symposium on the Electrophysiological Effects of Nicotine, Paris, France October 1978 19-20 (1979).

<sup>69</sup> Industry Comments at III-112 to III-121.

effect. Taste occurs principally in nerves on the tongue; smell, principally in those in the nose; and trigeminal effect, principally in those in the throat, upper respiratory tract, and nose. (Trigeminal effect refers to sensations such as "hot" or "cool" or "spicy"; it describes the "flavor" reaction to peppers, menthol, and even carbonated soda.)

Published literature in the 1960s and 1970s had explored the extent to which stimulation of these three senses -- taste, smell and trigeminal effect -- produced different electrical activity in the brain.<sup>70</sup> In the late 1970s, Dr. Gerd Kobal of the University of Erlangen-Nuremberg in Germany, with the aid of an "olfactometer" of his own design, had published the most advanced work on these flavor issues, which isolated differential electrical activity in the brain produced by smell and trigeminal stimulation.<sup>71</sup>

With Dr. Kobal's assistance, Philip Morris engineers constructed a similar "olfactometer," adding a computer control.

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<sup>70</sup> See, e.g., Allison T., Goff W.R. *Human Cerebral Evoked Responses to Odorous Stimuli*. *Electroencephalography and Clin. Neurophysiology* 23:558-560 (1967).

Smith D.B., Allison T., Goff W.R. *Human Odorant Evoked Responses: Effects of Trigeminal or Olfactory Deficit*. *Electroencephalography and Clin. Neurophysiology* 30:313-317 (April 1971).

<sup>71</sup> See Plattig K.H., Kobal G. *Spatial and Temporal Distribution of Olfactory Evoked Potentials and Techniques Involved in their Measurement* In: Lehmann D., Callaway E. (ed.) Human Evoked Potentials: Applications and Problems 285-302 (1979).

This equipment delivered precise quantities of the vapor phase<sup>72</sup> of various flavor compounds -- olfactory and trigeminal stimuli -- to the nasal cavity of a subject, and recorded the EEG reaction to these flavor sensations. This is the "olfactometer" referred to in Dr. Uydess' declaration.

Dr. Gullotta's "olfactometer" research thus investigated the manner in which "flavor" is experienced -- whether after a given compound is administered to the nasal cavity, its effects were olfactory (smell-related) or trigeminal. The studies attempted to determine whether people could discriminate between compounds that were olfactory (smell-related) and trigeminal, or among similar trigeminal stimulants.<sup>73</sup>

Contrary to Dr. Uydess' speculations, nicotine was never used in this "olfactometer" research by Dr. Gullotta.<sup>74</sup> Instead, the compounds studied included vanillin (vanilla), employed as a control because it operates only on the olfactory nerves, and

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<sup>72</sup> Dr. Uydess erroneously states that the "olfactometer" delivered an "aerosol." Uydess Declaration at 18, 19.

<sup>73</sup> This apparently is what Dr. Uydess refers to in his remarks about Philip Morris' "frustration" with smokers' verbal expression of the characteristics of their smoking experience, and its wish "to come up with a method to generate 'objective' (physical) data . . . ." Uydess Declaration at 18. For example, Dr. Gullotta's research established that EEG analysis could differentiate between closely-related tobacco flavorants, such as natural and synthetic menthols in varying proportions, even where an individual could not discriminate between them subjectively.

<sup>74</sup> See Uydess Declaration at 18, 20. On one or two occasions, researchers sought to administer cigarette smoke to a subject's nasal cavity via the "olfactometer," but the smoke interfered with the functioning on the equipment, and the efforts were not repeated.

carbon dioxide, similarly employed because it operates only on the trigeminal nerves (not, as Dr. Uydess suggests, because it is a component of cigarette smoke).<sup>75</sup> Other compounds studied included limonene (lemon), phenyl ethyl alcohol (synthetic rose), methyl salicylate (wintergreen), and dimethyl anthranilate (grape juice). Clearly, none of this work has any relevance to the jurisdictional issue in these proceedings.

Dr. Uydess has apparently been persuaded to speculate that Dr. Gullotta's research "possibly" established that nicotine is "addictive." Uydess Declaration at 18. He also reports his "understanding that some of the [EEG] responses observed by Dr. Gullotta after administration of various levels of nicotine, appeared to mimic those that had been reported in the literature for addictive substances like cocaine." Uydess Declaration at 20 (emphasis of hedge words added). These are deliberately inflammatory statements. They are not true. And they certainly do not support FDA's assertion of jurisdiction over cigarettes.

To be sure, Dr. Gullotta's basic research reported that nicotine has an EEG effect.<sup>76</sup> As stated above, this was

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<sup>75</sup> Dr. Uydess' failure to understand this most basic point about cigarette smoke highlights his lack of expertise in these areas. Again, he is simply not qualified to provide meaningful opinions on such matters.

<sup>76</sup> The effect was confirmed not by use of the "olfactometer," as suggested in Dr. Uydess' confused account, Uydess Declaration at 19, but rather by a different EEG protocol known as "Evoked Potential". Further, contrary to Dr. Uydess' account, the subjects in the study were not assigned a "task," id., nor were they asked to "interpret . . . their experiences," id. at 19-20.

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consistent with previously reported findings in the EEG literature.<sup>77</sup> But Dr. Gullotta was not asked to conduct EEG studies to determine whether nicotine was "addictive"; he did not do so; and, of course, nicotine's minor EEG effect does not make it "addictive."<sup>78</sup>

Dr. Uydess' highly-hedged statement suggesting that Dr. Gullotta's work could provide some basis for equating nicotine and cocaine is irresponsible in the extreme. Uydess Declaration at 20. Cocaine was not part of Dr. Gullotta's research: He did not study it; he drew no conclusions about it; and none of his work justifies any equation of nicotine and cocaine.

Dr. Gullotta did study the pharmacological effect of another substance on the central nervous system -- caffeine. In two different studies, Dr. Gullotta performed EEG analyses of the effect on human subjects of administration of amounts of caffeine roughly equal to that found in one or two cups of coffee. The results showed similar effects on the subject's EEG patterns as found with cigarette smoking -- hardly an indication that either substance is "addictive."

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It is clear that Dr. Uydess simply does not understand how Dr. Gullotta's EEG studies were conducted.

<sup>77</sup> See, e.g., Remond A., et al. The Action of Smoking on Visual Evoked Potentials, Biofeedback, EEG Changes and Autonomous Responses In: Remond A., Izard, C. (eds.) Electrophysiological Effects of Nicotine: Proceedings of the International Symposium on the Electrophysiological Effects of Nicotine, Paris, France, October 1978 19-20 (1979).

<sup>78</sup> See Industry Comments at III-60 to III-61.

In short, Dr. Gullotta's work at Philip Morris was basic research employing EEG techniques in response to similar work being done elsewhere. None of his research provides any basis for FDA's assertion of jurisdiction over cigarettes, or for the irresponsible assertion that nicotine is "like cocaine."

E. Dr. Uydess' "Hidden Company"

At various points in his statement, Dr. Uydess suggests that Philip Morris was engaged in secret "health-related" research entirely unrelated to nicotine. Uydess Declaration at 6, 21. Clearly such comments can have no impact on the jurisdictional question at issue in these proceedings.

Suffice it to say, none of this research was at all improper. For example, Philip Morris' interest in processes to remove nitrates from reconstituted tobacco sheet, in response to concerns of the Surgeon General and others, has hardly been a secret. Uydess Declaration at 4-5. Most notably, both the process that Dr. Uydess helped develop and the competing process Philip Morris has used to reduce nitrate levels over the last 20 years are the subject of public patents. Philip Morris' interest in this area only demonstrates that it will spend a great deal of time and money to reduce the production of certain smoke constituents which health officials have suggested might be the cause for concern.

Similarly, Dr. Uydess' ruminations about what he perceived to be an "inner company" within Philip Morris in which some research was conducted on a "need-to-know" basis can have no bearing on FDA's jurisdiction (or more accurately lack of jurisdiction) over the cigarettes Philip Morris produces. Uydess Declaration at 20, 22. As even Dr. Uydess concedes, the operations of virtually any large corporation -- and, we would venture, FDA as well -- are not known to all of its various employees. Uydess Declaration at 22. What is perhaps most remarkable about Dr. Uydess' speculations concerning the dissemination of internal research results is that he was not personally involved in most of the "sensitive" research he describes in his declaration; and yet he apparently believes he understands the goals, procedures and findings of those various research projects. One or the other of Dr. Uydess' "impressions" must be wrong. Actually, both are wrong: Those involved in the research conducted it in an appropriate manner; they simply did not run all of their findings before Dr. Uydess, who was hired to work on other, unrelated matters.

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As demonstrated above and in the documents submitted with these comments, Dr. Uydess' speculations, assumptions, and presumptions are so invalid -- and, in any event, so irrelevant -- that any effort by the Agency to rely upon them as a basis for FDA

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jurisdiction over cigarettes would itself be arbitrary and capricious.

### III. THE RIVERS DECLARATION

Because the issues presented by the declaration of Jerome Rivers, a former supervisor in Philip Morris' Blended Leaf Plant, are so clear-cut and capable of objective refutation, our comments on that document will be quite brief.

Mr. Rivers' declaration makes three essential allegations: first, that while he was working at Philip Morris' Blended Leaf Plant, that facility was monitoring or measuring for alkaloids or nicotine on a daily basis as part of the blended leaf manufacturing process and was using a gas chromatograph in the laboratory in the Blended Leaf Plant to do so (Rivers Declaration at 2-3); second, that Philip Morris had alkaloid or nicotine "standards or 'specs'" for the blended leaf product (Rivers Declaration at 3); and third, that Philip Morris' other reconstituted tobacco plant, the Park 500 facility at which a product commonly referred to as "reconstituted leaf" was made, also used a gas chromatograph to monitor or measure for alkaloids or nicotine in that process. Rivers Declaration at 4.

These allegations are false. As set forth in the accompanying affidavits of Jerry Bazemore and John Whitman, which address the specific practices at the Blended Leaf and Park 500 reconstituted tobacco manufacturing facilities:

1. At no point in the manufacture of blended leaf does the Blended Leaf Plant or its laboratory monitor or measure for alkaloids or nicotine -- whether by gas chromatograph or by any other instrument or device. Bazemore Affidavit ¶ 4; Whitman Affidavit ¶ 3.

2. Nor does Philip Morris have a "standard or 'spec'" for the alkaloid or nicotine content of the blended leaf product. Bazemore Affidavit ¶ 5; Whitman Affidavit ¶ 3. Mr. Rivers is thus flatly wrong when he charges that the Blended Leaf Plant conducted such nicotine testing, that there was a "standard or 'spec'" for nicotine, or that finished product was reprocessed when it was "out-of-spec" for nicotine. Bazemore Affidavit ¶ 5. Because there was no "spec" for alkaloids or nicotine, there was no "out-of-spec" for alkaloids or nicotine.

3. Mr. Rivers' hearsay account that Philip Morris was using a gas chromatograph at the Park 500 Plant "to measure the alkaloid content of the reconstituted leaf" is likewise untrue. The Park 500 facility did not, and does not, monitor or measure for alkaloids or nicotine in connection with the reconstituted leaf process -- whether by gas chromatograph or by any other instrument or device. Whitman Affidavit ¶ 3.

Contrary to Mr. Rivers' declaration, and as Philip Morris has previously stated publicly, nicotine in the tobacco used in Philip Morris' products is measured at only two points in the

cigarette manufacturing process -- before the tobacco materials are blended into cigarettes, and then after the tobacco materials have been made into finished cigarettes. Representative periodic sampling is done with respect to all tobacco materials that go into the cigarette manufacturing process -- natural leaf tobacco, expanded tobacco, as well as blended and reconstituted leaf. Such periodic sampling includes measurements of as many as 16 different characteristics of the tobacco materials, including alkaloids or nicotine. Subsequent to manufacture, representative samples of finished cigarettes are tested using the FTC-prescribed method for measuring "tar" and nicotine yields from smoke. None of these periodic sampling tests bears the remotest resemblance to Mr. Rivers' allegations of regular -- indeed, hourly -- monitoring of nicotine at the Blended Leaf Plant in order to manage the nicotine levels in the blended leaf process or product.

In short, Mr. Rivers is either grievously mistaken or deliberately stating something he knows to be untrue. In either case, as the accompanying affidavits demonstrate, it would be arbitrary and capricious -- if not outright irresponsible -- for the Agency to place any reliance at all on Mr. Rivers' statements.

#### IV. THE FARONE "REPORT"

The "report" by Dr. William Farone, a former Philip Morris employee who was discharged by the company in 1984, is essentially a rehash of prior charges made by various anti-tobacco critics. Philip Morris has already refuted most of these allegations and

speculations in its prior individual and joint industry submissions. In fact, most of Dr. Farone's more significant assertions are entirely undocumented. And where he does provide some citation, the documents and published literature he cites do not support his charges.

In the pages that follow, we will address a few points Dr. Farone asserts on the basis of certain specific Philip Morris documents.<sup>79</sup>

**A. Dr. Farone's Contention that Nicotine  
Is a Principal Reason People Smoke**

Dr. Farone makes repeated statements to the effect that the "cigarette industry" recognized or understood that consumers smoke solely because of the pharmacological properties of nicotine. Farone Statement at 1-3, 6-7. These statements are not supported by the documents Dr. Farone cites; and they are simply not true. As explained at greater length in the Industry Comments, consumers do not smoke cigarettes "nearly exclusively" for the pharmacological effects of nicotine. Rather, they smoke for many reasons, ranging from the flavor of tobacco smoke, to oral

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<sup>79</sup> The other leading cigarette producers are joining with Philip Morris in responding jointly to certain statements by Dr. Farone about the "industry" as a whole. In other instances, Dr. Farone has referred to documents of manufacturers other than Philip Morris -- and indeed to statements made by companies which do not produce cigarettes at all -- and has attempted to relate them to every company in "the industry." We again remind the Agency that any decision on FDA jurisdiction must be made on an individual product-by-product basis -- and then only on the basis of statements made to the public in connection with the marketing of that specific product.

gratification, to the ritual associated with lighting and holding a cigarette.<sup>80</sup>

The internal documents of Philip Morris employees cited by Dr. Farone as "evidence" that Philip Morris, or indeed "the industry" as a whole, believes consumers smoke solely for the pharmacological effects of nicotine simply do not provide any such "evidence" or any basis for FDA jurisdiction. For example, one 25-year old document cited by Dr. Farone as "evidence" that the industry believed people smoke for the pharmacological effects of nicotine<sup>81</sup> states that the reason "why people smoke" was not understood:

"Now we are beginning to concentrate on the smoker himself. We are addressing ourselves to that simple but fundamental question. 'Why do people smoke?' I must admit to some embarrassment when I say I don't know the answer to this question. It is even more embarrassing to the psychologists on my staff. But I can tell you this despite the voluminous research and pseudo-sophisticated theories, there is not a scientist alive who can give an explanation backed up by fact."<sup>82</sup>

<sup>80</sup> Industry Comments at III-69 to III-124.

<sup>81</sup> Farone Statement at 2-3.

<sup>82</sup> "Ryan/Dunn Alternate-Third Version of Board Presentation," at 6-7 (Fall 1969) (emphasis added). The suggestion that this 1969 presentation reflected a real understanding of why people smoke is further undermined by a 1973 book by the same author on smoker motivations in which he states:

"Clark L. Hull (1924) explained his work as a search for 'a clue to the charm which tobacco has for those accustomed to its use.' Today, almost a half century later, while smokers around the world are smoking cigarettes at the rate of three trillion ( $3 \times 10^{12}$ ) annually, we still seem a long  
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A 1980 memorandum from another Philip Morris scientist, in which the author only purports to express "my views," similarly shows uncertainty about the role of nicotine in smoking behavior. As the document explains:

"I believe that nicotine does play an important role in the smoking process. How important that role is remains to be determined."<sup>83</sup>

Dr. Farone's suggestion that by the 1970's the "tobacco industry" understood that smokers "required a minimal level of nicotine" and designed their products accordingly is likewise not supported by the "evidence" he cites.<sup>84</sup> Indeed, the Philip Morris document he cites does not even show that its author had concluded that nicotine was essential to smoking behavior.

The 1972 memorandum by Dr. Dunn actually reported on a conference of 25 "pharmacologists, sociologists, anthropologists, and a preponderance of psychologists," most of whom were academics, not industry employees. As stated in the memorandum, these scientists explored varying hypotheses about the reasons for smoking and the characteristics of smokers. The document reports on various views expressed at the conference, on Dr. Dunn's

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way from a generally accepted explanation for that charm."

Dunn W.L. (ed.) Smoking Behavior: Motives and Incentives 93 (1973) (emphasis added) (footnote omitted).

<sup>83</sup> Memorandum from J. Charles to R. Seligman, "Nicotine Receptor Program - University of Rochester," (March 18, 1980):

<sup>84</sup> Farone Statement at 1.

personal views, and on published literature concerning smoking behavior. The text of Dr. Dunn's memorandum itself makes clear that he was merely summarizing the hypotheses of the attendees at the conference.<sup>85</sup>

Dr. Farone's citation to the same 30-year-old patents previously cited by FDA is also irrelevant to the issue of "intended use." As even FDA has conceded, "the mere existence of a patent is not confirmation that the patent holder is using the invention claimed in the patent."<sup>86</sup> As discussed in the Industry Comments,<sup>87</sup> the fact that a scientist might have discovered a process for changing nicotine yields and patented that process in no way shows that his company was, or is, intent on adding nicotine to tobacco. And while the old patents cited theoretically could have been used to adjust nicotine yields, Philip Morris has never in fact used any of those patents to increase nicotine yields in commercial cigarettes. The Agency simply cannot rely on theoretical discussions of the possible addition of nicotine 25 to 30 years ago as "evidence" of the intent or practice of the cigarette manufacturers today.

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<sup>85</sup> Dunn W.L. "Motives and Incentives in Cigarette Smoking," at 4 (emphasis added).

<sup>86</sup> 60 Fed. Reg. 41,780.

<sup>87</sup> Industry Comments at IV-129 to IV-133.

**B. Low-Yield Cigarettes**

Dr. Farone suggests that a key objective of cigarette manufacturers was to design a cigarette with reduced "tar" levels while maintaining an unidentified "acceptable" level of nicotine. In so doing, Dr. Farone attempts to give credibility to speculation and innuendo previously set forth by FDA by packaging it as the thoughts of an industry "insider." Yet Dr. Farone, like FDA, provides no specific basis for his claims and ignores the historical and scientific facts refuting his theories as previously set forth in the January 1996 Industry Comments. We will not belabor them here. But a few points merit specific comment.

Dr. Farone repeatedly suggests that manufacturers use various tobacco technologies to produce cigarettes with unnaturally high levels of nicotine. In most cases, however, Dr. Farone does not provide any specifics, much less any sources, to support this charge. And in the few cases where he does cite some source, the facts -- as recorded in that very document -- undercut his "nicotine theory".

For example, Dr. Farone recycles FDA's theory that cigarette manufacturers use the very design features that have indisputably resulted in dramatic reductions in "tar" and nicotine yields over the last 40 years to "manipulate" the ratio of nicotine to "tar" in marketed cigarettes. Like FDA, Dr. Farone ignores the scientific fact that the physics of these advances in cigarette design do not reduce "tar" and nicotine yields to

precisely the same degree -- a fact recognized in some of the very documents cited by Dr. Farone.<sup>88</sup>

Dr. Farone also recycles the allegation made almost a year ago by Congressman Waxman that one of Philip Morris' cigarettes, Merit Ultra Light, "was introduced in 1981 with an elevated tar-to-nicotine ratio of 0.11" -- a ratio Dr. Farone apparently believes shows some manipulative intent. Dr. Farone, however, does not provide any further information on this brand; rather, he simply cites Congressman Waxman's remarks.

By relying entirely on Mr. Waxman, Dr. Farone thus ignores the facts previously set forth by Philip Morris that (a) Merit Ultra Light was an ultra-low yield product; (b) according to the FTC, the nicotine yield of a Merit Ultra Light in 1981 was only .3 mg; (c) the .3 mg nicotine yield of Merit Ultra Light was the 20th lowest among the 206 cigarette brands tested by the FTC that year; and (d) the .11 "nicotine-to-tar" ratio of the Merit Ultra Light likewise was equal to, or lower than, every one of the 50 other low-yield products on the market that year.

Dr. Farone's blind acceptance of Mr. Waxman's charge likewise ignores the fact, described in detail in the industry's prior comments, that slightly elevated "nicotine-to-tar" ratios are a natural consequence of the substantial reductions in both "tar" and nicotine achieved by modern filters. As the industry

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<sup>88</sup> See, e.g., "Filter Material Reduces CO/Tar Ratio Without Pressure Drop," Tobacco Reporter, 112(4):30-31 (April 1985). See also Industry Comments at IV-112 to IV-117; Philip Morris Comments at 40-44.

explained -- quoting published literature -- the more efficient filters and ventilation used on ultra-low yield products reduce "tar" to a somewhat greater degree than nicotine -- and hence increase slightly the "nicotine-to-tar" ratios of those ultra-low products.<sup>89</sup> Dr. Farone does not discuss or refute any of these facts; and his mere repetition of Mr. Waxman's unfounded charge does not give it any greater credibility.

Dr. Farone likewise fails to substantiate his contention that cigarette manufacturers have used flavors to "mask" enhanced nicotine deliveries. To "support" this contention, Dr. Farone cites only a single Philip Morris document which mentions that Philip Morris has used various flavors in its regular Merit brand.<sup>90</sup> But that document nowhere states that the purpose of those flavors was to mask higher nicotine yields. To the contrary, the document states that the purpose of the flavors was to provide an acceptable level of taste in a cigarette that had reduced tar and nicotine yields.<sup>91</sup>

Again, the facts undermine Dr. Farone's speculations. First, the regular Merit brand was, and still is, a low-yield cigarette. Using the same 1981 reference year, Merit, with a "tar" yield of 7 mg per cigarette and a nicotine yield of .5 mg per cigarette, was squarely in the low yield category (ranking

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<sup>89</sup> Industry Comments at IV-98 to IV-117.

<sup>90</sup> Farone Statement at 10-11.

<sup>91</sup> "Third Speaker, Merit Team" Remarks, Philip Morris, 2-3 (January 14, 1976).

50th lowest out of the 206 brands tested by the FTC that year in terms of its nicotine yield). The "nicotine-to-tar" ratio of Merit was thus .07 -- the level which FDA seems to believe is "natural".<sup>92</sup>

Indeed, that internal Philip Morris presentation further states that those at Philip Morris who developed Merit did not believe that it was a mere "nicotine delivery device" -- but rather that the explanations for the smoking habit were much more complex:

"But what do smokers get out of cigarettes? We know it is a mistake to look for one source of the satisfaction of smoking. For example, the nicotine in tobacco smoke is often singled out, and it does act as a mild stimulant and a mild relaxant. In some way its moderate effects can be similar to those of coffee, tea, or cocoa.

"But nicotine is an inexpensive tasteless constituent that can easily be consumed as a pill or in chewing gum and candy. In fact, those methods have been tested and they haven't been satisfying to smokers.

"Obviously other satisfactions are also involved. They include -- to a greater or lesser degree depending on the individual smoker -- the oral satisfaction of puffing on a cigarette and the tactile sensations of handling it.

"The original smokers, Indians, and more recently a number of poets expressed the belief that cigarette smoke offers passive satisfaction to people such as they may get from watching a sunset or a crackling fireplace.

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<sup>92</sup> Another way of looking at this undeniable fact is that, unlike the Merit Ultra Light which had the greater degree of filtration, and ventilation of an ultra-low product which naturally increases a "nicotine-to-tar" ratio, the regular Merit had a less dense filter which allowed more of both "tar" and nicotine to come through.

"But basically cigarettes provide a fundamental pleasure -- the simple enjoyment of the flavor of tobacco smoke.

"Since the earliest days in the history of tobacco, flavor has been a critical factor.

"Europeans first enjoyed tobacco in cigars and pipes. Because of flavor, cigar leaf from certain climates became preferred to others, and to this day tobacconists and pipe smokers constantly experiment with blends to achieve different flavors.

"Cigarettes started to gain popularity in England in the latter half of the last century, and again flavor was significant.

"Through the years, the flavor of cigarettes has been improved with the development of new strains of tobacco and, more recently, filtration and new blends. And the taste preferences of smokers have become much more refined as our cigarettes have become better. . . .

"To a few, like the social smokers who light up cigarettes only at parties, the tactile sensation of holding and handling something seems to be the primary satisfaction they derive.

"But the common denominator among the overwhelming majority of smokers is the enjoyment of flavor. This knowledge guided Philip Morris scientists as they achieved a great flavor breakthrough."<sup>93</sup>

Significantly, while the document goes on to discuss the fact that these flavor packages could compensate to some extent for the fact that the "tar" yield of the regular Merit was relatively low, there is not one word about the nicotine yield of that cigarette. The whole thrust of the document was that nicotine, while perhaps one component to some of the satisfaction

<sup>93</sup> Merit Team Second Speaker (Jan. 14, 1976) at 1003288908-910.

of some smokers, was not the critical component to those who chose Merit over other cigarettes.

Again, Dr. Farone's allegations are undercut by the very documents he cites.

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As shown above, and in the detailed comments filed last January, Dr. Farone's rehash of charges made by a Congressman or an undocumented newspaper article adds nothing to the validity of those accusations. However much the Agency may want to regulate cigarettes -- however much it may want to cloak its abrupt reversal of 90 years of congressional, judicial and FDA precedent with "newly discovered evidence" -- it would be arbitrary and capricious for the Agency to adopt as gospel such patently untrue assertions simply because a single researcher, who was discharged from a tobacco company 12 years ago, has now, without any specifics, recycled those charges. In FDA rulemaking as well as third-grade arithmetic, two times zero still equals zero.

#### CONCLUSION

The Agency's decision to reopen this record to allow the staff to add these three declarations -- which the staff apparently has been soliciting for months -- says far more about FDA's apparent recognition that it does not have an adequate factual (or legal) basis for its assertion of jurisdiction over cigarettes than it does about the practices or products of any cigarette manufacturer. The Agency's subsequent refusal to

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release the prior statements of these former employees on the same subjects -- as well as any coaching by the staff that may have prompted them -- is unworthy of an administrative body which claims to seek scientific truth. Such an attempt to salt the record in such a belated manner cannot succeed.

INDEX OF ARTICLES, REFERENCES & SOURCES  
CITED IN THE COMMENTS OF PHILIP MORRIS INCORPORATED  
ON STATEMENTS FILED WITH THE FDA ON MARCH 18, 1996

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