

**COMMENT SUBMITTED IN RESPONSE TO FDA QUESTIONS ON MENTHOL POSED IN ITS
ADVANCED NOTICE OF POTENTIAL RULEMAKING**

Docket No. FDA-2013-N-0521

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A. TOBACCO PRODUCT STANDARDS

1. Should FDA consider establishing a tobacco product standard for menthol in menthol cigarettes? If so, what allowable level of menthol (e.g., maximum or minimum) would be appropriate for the protection of the public health?

Rather than establishing a product standard, the FDA should prohibit the use of menthol and menthol analogs that have similar effects as menthol in cigarettes and all tobacco products. The FDA was granted the authority¹ to take action to prohibit the use of menthol altogether. The reasons for this recommendation are outlined in an earlier public comment (www.regulations.gov identifier 1jx-85zp-r17p) submitted in response to the Citizen's Petition on Menthol, which is reproduced here:

COMMENT ON CITIZEN PETITION ASKING THE U.S. FOOD AND DRUG ADMINISTRATION TO
PROHIBIT MENTHOL AS A CHARACTERIZING FLAVOR IN CIGARETTES [*]

Docket ID: FDA-2013-P-0435

June 19, 2013

Rather than prohibiting the use of menthol "as a characterizing flavor" as requested in the Citizen Petition, the FDA should simply prohibit the use of menthol (and menthol analogs) in cigarettes and, as it asserts jurisdiction over other tobacco products, those products as well.

There are two reasons for pursuing a prohibition.

First, "characterizing flavor" is not defined in the Family Smoking Prevention and Tobacco Control Act and the de facto definition of "characterizing flavor" that the FDA has applied to other additives (such as chocolate, licorice, and strawberry) that are included in the Act is that products containing these additives not be advertised using words as containing these additives. The FDA has taken no action to limit the actual use of these additives in cigarettes (or any other tobacco products). Thus, if the FDA applies the same de facto definition for menthol "as a characterizing flavor," cigarette companies could keep using menthol at the same levels in cigarettes as they are today, simply drop the word "menthol" from the packaging and advertising, and keep selling the cigarettes in color coded green packages.[†]

Second, should the FDA decide to prohibit the use of menthol above a certain concentration as a "characterizing flavor" the Agency would have to develop a methodology for setting the level of menthol that constituted a "characterizing flavor." Because of the complex

¹ Family Smoking Prevention and Tobacco Control Act sections 907(a)(1)(A) and 907(e)(3).

effects of menthol on the sensation of smoking as well as its complex interaction with nicotine (documented in the TPSAC report on menthol, the Citizen Petition, as well as the broader scientific literature) there is a good chance that it would be impossible to define an absolute level of menthol that smokers would “taste” that would be independent of all the other ingredients and additives in cigarettes (and other tobacco products). Such a process could take years, during which time the cigarette companies could continue making and promoting menthol cigarettes despite the fact that, as TPSAC noted, “Removal of menthol cigarettes from the marketplace would benefit public health in the United States.”[‡]

The FDA should simply use the information in the TPSAC report, the Citizen Petition, and the scientific evidence that continues to accumulate that menthol is more than just a “flavor,” but serves a wide range of functions to recruit youth to smoking and discourage quitting,[§] not just among one or another “target” group but among broad elements of the population.

Based on the available scientific evidence, a decision to prohibit the use of menthol and menthol analogs in cigarettes (and, when the FDA takes jurisdiction, other tobacco products) is clearly justified and easier to defend than trying to set an absolute level of menthol at which it becomes a “characterizing flavor.”

[*] In addition to in the FDA docket, the petition is available at <http://www.publichealthlawcenter.org/sites/default/files/tclc-fdacitizenpetition-menthol-2013.pdf>

[†] As detailed in my Comment on Docket No. FDA-2012-D-0071, Draft Guidance for Industry: Modified Risk Tobacco Product Applications, the FDA has taken no action to stop the companies from replacing the prohibited terms “light” and “mild” with color coded packages transmitting the same information, so there is no reason to expect that the FDA would treat menthol any differently.

[‡] Tobacco Products Scientific Advisory Comm., U.S. Food & Drug Admin., Menthol Cigarettes and Public Health: Review of the Scientific Evidence and Recommendations 220 (2011), available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterial/TobaccoProductsScientificAdvisoryCommittee/UCM269697.pdf> (final as reviewed and approved by the TPSAC on July 21, 2011) , page 225.

[§] See, for example, Levy, et al., Quit attempts and quit rates among menthol and nonmenthol smokers in the United States. *Am J Public Health*. 2011;101(7):1241-7 and Levy, et al, Modeling the Future Effects of a Menthol Ban on Smoking Prevalence and Smoking-Attributable Deaths in the United States. *Am J Pub Health* 2011;101(7):1236-40.

2. Rather than a tobacco product standard for menthol in menthol cigarettes, should FDA consider a tobacco product standard for any additive, constituent, artificial or natural flavor, or other ingredient that produces a characterizing flavor of menthol in the tobacco product or its smoke?

As noted above, menthol and all menthol analogs that have similar effects should be prohibited.

Additional evidence for prohibiting menthol and menthol analogs is presented in the WHO Framework Convention on Tobacco Control's Partial Guidelines for Implementation of Articles 9 and 10,² which addresses the importance of regulating ingredients aimed at reducing tobacco product attractiveness in order to help reduce the prevalence of tobacco use and dependence among new and continuing users. The guidelines stated that attractiveness and its impact on dependence should be taken into account when considering regulatory measures. In its discussion preceding its Recommendation 3.1.2.2 urging the prohibition of "ingredients that may be used to increase palatability in tobacco products," the FCTC Guidelines state:

The harsh and irritating character of tobacco smoke provides a significant barrier to experimentation and initial use. Tobacco industry documents have shown that significant effort has been put into mitigating these unfavourable characteristics. Harshness can be reduced in a variety of ways including: adding various ingredients... [or] balancing irritation alongside other significant sensory effects... Masking tobacco smoke harshness with flavours contributes to promoting and sustaining tobacco use. Examples of flavouring substances include... menthol.³

3. If a tobacco product standard for menthol in menthol cigarettes were to be established, should FDA consider issuing regulations to address menthol in other tobacco products besides cigarettes? If so, what other tobacco products with menthol should be regulated: All tobacco products, just all combusted tobacco products, or some other category or group of tobacco products? If not, what distinctions should be made between products?

The effects of menthol on other forms of tobacco use as well as its interaction with nicotine are likely similar to cigarettes, particularly for other inhaled products (including e-cigarettes). The FDA should ban menthol and menthol analogs from all other products over which the FDA has or takes jurisdiction (including little cigars and e-cigarettes).

4. If a product standard prohibiting or limiting menthol were to be established, what length of time should manufacturers be provided to achieve compliance with the standard? If a product standard prohibiting or limiting menthol were to be established, would a stepped approach in which the level of menthol was gradually reduced be appropriate for the protection of the public health?

A stepped approach should be avoided, since it will give the cigarette companies time to slowly convert menthol smokers to other forms of cigarettes. A one-step change will maximize the probability that people will simply stop smoking. For the same reasons, the time for the changeover should be short, no more than one year.

The fact that a possible menthol ban has been discussed since at least 2009, with the TPSAC report issued in 2011, has provided the tobacco companies more than enough advance notice that a menthol ban was possible.

5. If a product standard limiting menthol were to be established, are there alternatives that could be substituted by manufacturers to maintain the effect or appeal of menthol to menthol cigarette smokers and potential initiators? If so, what are these substitutes? Should they be regulated if menthol is regulated; and if so, how should they be regulated? If not, what distinctions should be made between menthol and potential substitutes?

² http://www.who.int/fctc/guidelines/Guideliness_Articles_9_10_rev_240613.pdf

³ http://www.who.int/fctc/guidelines/Guideliness_Articles_9_10_rev_240613.pdf

All analogs of menthol with similar anesthetic properties and similar interactions with nicotine should be prohibited until and unless companies submit new product applications supported by strong evidence that the new additive would not create the same risks for initiation and inhibited cessation as menthol currently creates. When considering a new product application, the FDA must determine whether the marketing of that product “is appropriate for the protection of the public health,” which must be “determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and taking into account – (A) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and (B) the increased or decreased likelihood that those who do not use tobacco products will start using such products.”⁴ In evaluating such claims the FDA should pay attention to whether or not these studies are adequately powered to detect the kind of small changes (i.e., a few percent change in initiation or quitting). Because the central assertion of such studies would be that there is *no effect* rather than seeking to reject the null hypothesis of no effect (which is more common in therapeutic trials), the required power should be comparable to the Type I error normally used in therapeutic trials (i.e., $\alpha = 0.05$).

This issue is addressed in more detail in the public comment I submitted on Substantial Equivalence, which is available on Regulations.gov at 1jw-82jq-ae81,⁵ which is being submitted again in response to the present request for public comment.

B. SALE AND DISTRIBUTION RESTRICTIONS

1. Should FDA consider establishing restrictions on the sale and/or distribution of menthol cigarettes? If so, what restrictions would be appropriate and what would be the impact on youth or adult smoking behavior, initiation, and cessation?

As noted above, menthol and its analogs should be banned, making restrictions on sale and/or distribution unnecessary.

Menthol cigarettes increase smoking initiation⁶ and decrease cessation.⁷ Therefore, if menthol were banned, smoking initiation would decrease and smoking cessation would increase, resulting in an overall reduction in smoking prevalence and the associated disease, death, and costs.

⁴ FSPTCA section 910(c)(4).

⁵ Glantz S. RE: Guidance for Industry and Food and Drug Administration Staff; Section 905(j) Reports: Demonstrating Substantial Equivalence for Tobacco Products; Availability (Document ID FDA-2010-D-0635-0001). December 15, 2012. Available on www.regulation.gov at 1jw-82jq-ae81.

⁶ Hersey, JC, et al., “Are menthol cigarettes a starter product for youth?”, *Nicotine & Tobacco Research*, 8(3): 403-413, 2006; Klausner, K, “Menthol cigarettes and smoking initiation: a tobacco industry perspective,” *Tobacco Control* 20 (Supp. 2), ii12-ii19, 2011; TPSAC, 2011 (pages 215-19); Nonnemaker, et al., “Initiation with menthol cigarettes and youth smoking uptake,” *Addiction* 108: 171-178, 2012.

⁷ Jennifer L. Pearson et al., A Ban on Menthol Cigarettes: Impact on Public Opinion and Smokers’ Intention to Quit, *Am. J. Pub. Health* 102(11) e107, e112, 2012; Okuyemi, K S, Ahluwalia, J S, Ebersole-Robinson, M, Catley, D, Mayo, M S, & Resnicow, K. Does menthol attenuate the effect of bupropion among African American smokers? *Addiction*, 2003: 98(10), 1387-1393; Okuyemi, K S, Faseru, B, Sanderson Cox, L, Bronars, C A, & Ahluwalia, J S. Relationship between menthol cigarettes and smoking cessation among African American light smokers. *Addiction* 2007: 102(12), 1979-1986; Harris, K J, Okuyemi, K S, Catley, D, Mayo, M S, Ge, B, & Ahluwalia, J S. Predictors of smoking cessation among African-Americans enrolled in a randomized controlled trial of bupropion. *Preventive Medicine*, 2004: 38(4), 498-502.

A model⁸ that projected the impact that a US menthol ban would have on smoking prevalence and smoking-attributable deaths found that in a scenario in which 30% of menthol smokers quit and 30% of those who would have initiated as menthol smokers do not initiate, by the year 2050 the relative reduction in smoking prevalence would be 10% overall and 25% for African Americans, and 633,000 overall deaths and 237,000 African American deaths would be averted. Even if a menthol ban were associated with only a 10% increase in cessation and a 10% reduction in initiation, by 2050 the relative reduction in smoking prevalence would be 4% overall and 9% for African Americans, with 323,000 overall deaths and 92,000 African American deaths averted. These are gigantic health benefits that would easily swamp any modest costs of implementing a ban on menthol.

In a 2012 survey of menthol smokers, 36.5% reported that if menthol in cigarettes were prohibited, they would try to quit smoking, and more than 17% said they would not consider using non-menthol cigarettes.⁹ Another survey found that 38.9% of menthol smokers would quit in response to a prohibition of menthol cigarettes. The intent to quit was even higher among African American menthol smokers (44.5%) and female menthol smokers (44.0%).¹⁰ Additional information was provided to TPSAC.¹¹

2. Should FDA consider establishing restrictions on the advertising and promotion of menthol cigarettes? If so, what restrictions would be appropriate and what would be the impact on youth or adult smoking behavior, initiation, and cessation?

Because menthol cigarettes would no longer be legal, the FDA should prohibit advertising of menthol cigarettes, including promotion of brands with colored and other package indicators and advertising images that suggested menthol cigarettes.

Prohibiting color coding of packages and other similar strategies will be critical to avoid the situation that exists with light and mild cigarettes, where the cigarette companies simply color coded packs to transmit the same information that is prohibited by law.¹² (The FDA should initiate an enforcement action to stop this blatant flaunting of law and FDA regulations.) This issue is discussed at length in my earlier public comment on guidelines for modified risk products¹³ which is included in this comment by reference.

⁸ Levy, DT, Pearson, JL et al., "Modeling the Future Effects of a Menthol Ban on Smoking Prevalence and Smoking-Attributable Deaths in the United States." *Am J Public Health*. 2011 July; 101(7): 1236–1240.

⁹ O'Connor RJ, "What would menthol smokers do if menthol in cigarettes were banned? Behavioral intentions and simulated demand," *Addiction*, 107(7):1330-8, 2012.

¹⁰ Jennifer L. Pearson et al., A Ban on Menthol Cigarettes: Impact on Public Opinion and Smokers' Intention to Quit, 102(11) *Am. J. Pub. Health* 2012: e107-e112.

¹¹ Hartman A. What Menthol Smokers Report They Would Do If Menthol Cigarettes Were No Longer Sold 3,6 (2011) available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM243628.pdf> (public submission to the FDA Tobacco Product Scientific Advisory Committee, for the Feb. 10, 2011 meeting).

¹² Connolly, G and Alpert, H, "Has the tobacco industry evaded the FDA's ban on 'Light' cigarette descriptors?" *Tob Control*, 2013. <http://tobaccocontrol.bmj.com/content/early/2013/03/01/tobaccocontrol-2012-050746.full.pdf+html>

¹³ Glantz S. Comment on Docket No. FDA-2012-D-0071 Draft Guidance for Industry: Modified Risk Tobacco Product Applications. June 2, 2012.

As discussed below, such a prohibition would also reduce demand, including any potential demand for smuggled menthol cigarettes.

C. OTHER ACTIONS AND CONSIDERATIONS

1. Are there other tobacco product standards, regulatory, or other actions that FDA could implement that would more effectively reduce the harms caused by menthol cigarette smoking and better protect the public health than the tobacco product standards or regulatory actions discussed in the preceding questions?

No, at least not related to menthol.

2. To the extent that you have identified a tobacco product standard or other regulatory action in response to the prior questions, please provide additional information and comments on:

2.1 Is compliance with the tobacco product standard or other regulatory action you identified technically achievable?

Yes. In fact an outright menthol ban would be the simplest to implement and enforce, both in terms of ensuring that the tobacco products are free of menthol, and also because an outright ban would make smuggling more difficult.

An outright ban would also resolve the problems raised in the Indonesia WTO dispute over the FDA's ban of clove cigarettes because it would eliminate the predicate for Indonesia's claim that the US is discriminating against clove cigarettes because the US still allows the sale of menthol cigarettes.

2.2 How FDA would structure a corresponding rule to maximize compliance, facilitate enforcement, and otherwise maximize public health benefits?

As noted above, a menthol ban would be easiest to implement and enforce and would have the maximum public health benefit by reducing initiation and increasing cessation.

3. If menthol cigarettes could no longer be legally sold, is there evidence that illicit trade in menthol cigarettes would become a significant problem? If so what would be the impact of any such illicit trade on public health? How would any such illicit trade compare to the existing illicit trade in cigarettes?

While there is no doubt some illicit trade in tobacco products in general, all the independent (i.e., not from tobacco companies and their political allies) estimates are that these levels are low, generally a few percent of the market.¹⁴ It is hard to envision a situation in which the illicit trade could grow to the point that it would support the large market share that menthol cigarettes occupy.

As discussed above, ending menthol cigarettes would also lead many smokers to quit, further reducing market for menthol cigarettes. The fact that advertising of menthol cigarettes would end because they were no longer legally available would also reduce demand. Any analysis of alleged smuggling should take this fact into account.

¹⁴ For domestic results see, for example, Alamar B, Mahmoud L, Glantz S. Cigarette Smuggling in California: Fact and Fiction. Center for Tobacco Control Research and Education, UC San Francisco, <http://escholarship.org/uc/item/4fv0b2sz> and for international results see Joossens L., Raw, M. From cigarette smuggling to illicit tobacco trade."Tobacco Control 2012;21:230-234.

A complete ban would be easier to enforce than a partial ban or product standard because under a complete ban, no menthol cigarettes would be in the legal market to provide cover for smuggled cigarettes. Thus, any menthol cigarettes for sale anywhere would have to have been smuggled or illegally produced.

The tobacco companies will no doubt claim that smuggling will be rampant. Because producing enough menthol cigarettes to have a substantial effect on the market would have to be done on an industrial scale, they would have to be involved (as they have been documented to be in mass international smuggling of cigarettes¹⁵), which would be easy for the FDA to detect as part of its efforts to monitor manufactures.

If the FDA is concerned about smuggling, it should require pack-by-pack tracking of cigarettes from the manufacturer through the point of sale together with high-tech sales stamps as have been developed in California and elsewhere. (Indeed, this would be a good idea in any event.)

4. What additional information and research beyond that described in the evaluation is there on the potential impact of sale and distribution restrictions of menthol cigarettes on specific subpopulations, such as those based on racial, ethnic, socioeconomic status, and sexuality/gender identity?

The evidence that menthol increases tobacco use among African Americans, Hispanics, women, and youth is discussed above, so a menthol ban will particularly benefit those populations.

The FDA should consider the immediate (short term) changes in smoking behavior and health effects, particularly those related to cardiovascular disease, low birthweight, and respiratory problems that occur after quitting smoking¹⁶ or implementing smokefree laws¹⁷ in any cost-benefit analysis it does of a rule banning menthol. In addition, analyses of the effects of implementing large scale state tobacco control programs provide direct estimates of the dynamic effects of reducing cigarette consumption on health care costs that show that reductions in smoking are accompanied by rapid changes in health care costs that grow over time.¹⁸ Including these short-term (and growing) effects is particularly important because of time discounting of future health benefits; ignoring these immediate benefits would lead the FDA to substantially underestimate the benefits of eliminating menthol.

¹⁵ Campaign for Tobacco-Free Kids, *Illegal Pathways to Illegal Profits: The Big Cigarette Companies and International Smuggling*, 2003; The International Consortium of Investigative Journalists, "Global reach of tobacco company's involvement in cigarette smuggling exposed in company papers," Feb. 2, 2000. <http://www.icij.org/node/460/global-reach-tobacco-companys-involvement-cigarette-smuggling-exposed-company-papers>.

¹⁶ Lightwood J, Glantz S. Short-term Economic and Health Benefits of Smoking Cessation: Myocardial Infarction and Stroke. *Circulation*. 1997;96:1089-1096; Lightwood J, Glantz S. Short-term Economic and Health Benefits of Smoking Cessation: Myocardial Infarction and Stroke. *Circulation*. 1997;96:1089-1096.

¹⁷ Tan C, Glantz S. Association Between Smoke-Free Legislation and Hospitalizations for Cardiac, Cerebrovascular, and Respiratory Diseases : A Meta-Analysis. *Circulation*. 2012;126:2177-2183. doi: 10.1161/CIRCULATIONAHA.112.121301; Glantz SA, Gibbs E. Changes in ambulance calls after implementation of a smoke-free law and its extension to casinos. *Circulation*. 2013 Aug 20;128(8):811-3. doi: 10.1161/CIRCULATIONAHA.113.003455. Epub 2013 Aug 5.

¹⁸ Lightwood J, Glantz S. Effect of the Arizona tobacco control program on cigarette consumption and healthcare expenditures. *Soc Sci Med*. 2011;72(2):166-72 (PMC 3603372); Lightwood J, Glantz SA. The effect of the California tobacco control program on smoking prevalence, cigarette consumption, and healthcare costs: 1989-2008. *PLoS One*. 2013;8(2):e47145 (PMC 3572143); Lightwood JM, Dinno A, Glantz SA. Effect of the California tobacco control program on personal health care expenditures. *PLoS Med*. 2008;5(8):e178 (PMC 2522256)

5. To what extent are you aware of current (within the past 5 years) advertising and/or promotion of menthol cigarettes that have targeted specific communities, subpopulations, and locations, beyond that described in the evaluation?

I am personally aware of targeting of African American and Hispanic communities from simply walking around neighborhoods with concentrations of these people and of targeting of youth by walking past convenience stores near schools. Because I am aware of the fact that other public health commenters with specific technical expertise in this area are planning submissions, I am not providing scientific citations in response to this question.

6. Might any current advertising or other marketing or public statements concerning menthol cigarettes, or menthol in other tobacco products, constitute reduced risk claims?

It is well established that the public believes that menthol cigarettes are “safer.” This impression has been built through decades of advertising imagery which constitute implicit reduced risk claims. Because I am aware of the fact that other public health commenters with specific technical expertise in this area are planning submissions, I am not providing scientific citations in response to this question.

THE DIRECT HEALTH EFFECTS OF MENTHOL AS AN ADDITIVE

In its 2013 “Preliminary Scientific Evaluation of the Possible Public Health Effects of Menthol Versus Nonmenthol Cigarettes”¹⁹ the FDA concluded that menthol did not have any direct adverse health effects.

While the dominant effect of menthol is that it helps recruit new smokers and reduces cessation, Philip Morris’ “Project Mix,” a large study of the effects of a wide range of additives on the constituents of cigarette smoke and smoke toxicity, found that adding menthol to test cigarettes significantly increases particulate matter in the smoke (which has direct adverse health effects) as well as several other smoke constituents. Wertz, et al²⁰ used previously secret tobacco industry documents to examine the Project Mix protocols as well as results that Philip Morris did not publish. This analysis revealed that, in contrast to the way that the results were represented in Philip Morris’ published papers on Project Mix,²¹ the results showed several adverse toxicological effects associated with adding menthol to cigarettes. (See

¹⁹ Food and Drug Administration (July 2013)

<http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PeerReviewofScientificInformationandAssessments/UCM361598.pdf>

²⁰ Wertz MS, Kyriss T, Paranjape S, Glantz SA (2011) The Toxic Effects of Cigarette Additives. Philip Morris’ Project Mix Reconsidered: An Analysis of Documents Released through Litigation. PLoS Med 8(12): e1001145. doi:10.1371/journal.pmed.1001145

²¹ Philip Morris’ published Project Mix papers are: Carmines EL (2002) Evaluation of the potential effects of ingredients added to cigarettes. Part 1: cigarette design, testing approach, and review of results. *Food Chem Toxicol* 40: 77–91; Rustemeier K, Stabbert R, Haussmann HJ, Roemer E, Carmines EL (2002) Evaluation of the potential effects of ingredients added to cigarettes. Part 2: chemical composition of mainstream smoke. *Food Chem Toxicol* 40: 93–104; Roemer E, Tewes FJ, Meisgen TJ, Veltel DJ, Carmines EL (2002) Evaluation of the potential effects of ingredients added to cigarettes. Part 3: in vitro genotoxicity and cytotoxicity. *Food Chem Toxicol* 40: 105–111. 18; Vanscheeuwijck PM, Teredesai A, Terpstra PM, Verbeeck J, Kuhl P, et al. (2002) Evaluation of the potential effects of ingredients added to cigarettes. Part 4: subchronic inhalation toxicity. *Food Chem Toxicol* 40: 113–131.

Figure 4, Table 1, and Table S-3 of Wertz, et al for specific constituents and toxicological effects that are increased; “Ingredient Group 3” is primarily menthol.)

The FDA should also pay particular attention to the Wertz, et al paper since it documents how Philip Morris changed its analytical protocol in a way to obscure the fact that additives increased the toxicity of cigarette smoke after its initial analysis revealed that they did. Specifically, Philip Morris found that the additives (including menthol) increased the amount of total particulate matter that the cigarettes produced, as well as increased the amounts of many other toxins. The increase in particulate matter was often larger than the increase in the other toxins, so, in its published papers, Philip Morris normalized toxin levels by the absolute level of total particulate matter. While both the numerators (the other toxins) and the denominators (total particulate matter) increased, the increase in the denominator was often larger than the numerator, which reduced the ratio and so made it look like the additives reduced toxin levels when they often *increased* them.

For similar reasons (detailed in Wertz, et al), a total particulate matter adjustment led the animal toxicology studies to underestimate adverse biological effects.

Philip Morris also used small numbers of animals, which led to underpowered studies and so obscured many health effects.

Both Philip Morris²² and Philip Morris International²³ submitted letters to the editor strenuously objecting to Wertz, et al’s conclusions. Careful assessment of these responses²⁴ reveals, however, that both Philip Morris and Philip Morris International failed to address the fundamental issues raised in Wertz, et al’s reanalysis of the Project Mix protocols and data.

British American Tobacco published a similar series of studies²⁵ that, if interpreted properly, show similar adverse consequences from adding menthol to cigarettes. These papers are also discussed in Wertz, et al.

²² Comments from Michael J. Oldham Ph.D., Associate Principal Scientist, and Willie J. McKinney Jr., Ph.D., D.A.B.T., Director, Product Integrity, Altria Client Services, March 5, 2012, re: Wertz et al. 2011 “The Toxic Effects of Cigarette Additives. Philip Morris’ Project Mix Reconsidered: An Analysis of Documents Released through Litigation”, PLoS Medicine, December 2011, Vol 8(12).

<http://www.plosmedicine.org/annotation/listThread.action?root=13441> (This comment is appended to the PDF of Wertz, et al that was submitted to the docket.)

²³ Comments from Ruth Dempsey, Chief Scientist Operations Philip Morris International, December 22, 2011, re: Wertz et al, 2011 “The Toxic Effects of Cigarette Additives. Philip Morris’ Project Mix Reconsidered: An Analysis of Documents Released through Litigation”, PLoS Medicine, Dec 2011, vol 8(12) (published online on December 21, 2011). <http://www.plosmedicine.org/annotation/listThread.action?root=17399>. (This comment is appended to the PDF of Wertz, et al that was submitted to the docket.)

²⁴ Wertz M, et al. Philip Morris USA’s letter (also) continues business as usual.

<http://www.plosmedicine.org/annotation/listThread.action?root=13441>; Wertz M, et al. Philip Morris’ letter continues business as usual <http://www.plosmedicine.org/annotation/listThread.action?root=17399> (These responses are appended to the PDF of Wertz, et al that was submitted to the docket.)

²⁵ Baker RR, Massey ED, Smith G. An overview of the effects of tobacco ingredients on smoke chemistry and toxicity. Food Chem Toxicol. 2004;42 Suppl:S53-83; Baker RR, Pereira da Silva JR, Smith G. The effect of tobacco ingredients on smoke chemistry. Part I: Flavours and additives. Food Chem Toxicol. 2004;42 Suppl:S3-37; Baker RR, Pereira da Silva JR, Smith G. The effect of tobacco ingredients on smoke chemistry. Part II: casing ingredients. Food Chem Toxicol. 2004;42 Suppl:S39-52

The Project Mix studies were conducted in anticipation of eventual FDA regulation of cigarettes, so should be viewed as advocacy efforts rather than objective science. A search of the internal industry documents found little genuine internal industry research on the disease-inducing effects of menthol.²⁶ Most information in the tobacco industry documents comprises reviews of the published biomedical literature, from which the companies concluded that menthol did not have any direct disease-inducing effects. Evidence that contradicted this conclusion was downplayed. Except for one study, there was no evidence of the companies following up on positive findings in the literature with their own studies. In one case, results were presented at a public scientific meeting concluding that 'There were no effects from addition of menthol to test or reference cigarettes', when a company's internal pathology analysis contradicted this statement. The fact that the available industry documents suggest that tobacco companies conducted little research on the potential disease-inducing effects of menthol and did not pursue studies that suggested adverse effects should add to the skepticism with which the FDA views any industry submissions on health effects.

It is important that the FDA be conscious of these misleading strategies because they are likely to appear in submissions that the tobacco companies make to the FDA in this and other dockets. The FDA should not take the conclusions in these industry studies at face value, but rather use it to support banning menthol.

²⁶ Salgado MV, Glantz S. Direct disease-inducing effects of menthol through the eyes of tobacco companies. *Tob Control*. 2011 May;20 Suppl 2:ii44-8. doi: 10.1136/tc.2010.041962.