

**Draft Guidance for Industry and FDA Staff  
“Harmful and Potentially Harmful Constituents”  
In Tobacco Products as Used in  
Section 904(e) of the Federal Food, Drug  
And Cosmetic Act**

**FDA-2010-D-0281**

**Comments Regarding Draft Guidance**

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## INTRODUCTION

The Family Smoking Prevention and Tobacco Control Act was signed into law by the President on June 22, 2009 (FSPTCA). The FSPTCA amended the Federal Food, Drug and Cosmetic Act (as amended, the Act). Section 904(e) of the Act provides “[n]ot later than 24 months after the date of enactment of the Family Smoking Prevention and Tobacco Control Act, the Secretary shall establish, and periodically revise as appropriate, a list of harmful and potentially harmful constituents, including smoke constituents, to health...”

On June 10, 2010, the Food and Drug Administration, Center for Tobacco Products (FDA-CTP) announced “the availability of a draft guidance for industry and FDA staff (Draft Guidance) entitled “‘Harmful and Potentially Harmful Constituents’ in Tobacco Products as Used in Section 904(e) of the Federal Food, Drug and Cosmetic Act.”

In meetings on June 8-9, 2010 and July 7, 2010, The Tobacco Product Constituents Subcommittee (Constituents Subcommittee) of the Tobacco Products Scientific Advisory Committee (TPSAC) received presentations and held discussions “on the development of a list of harmful or potentially harmful constituents, including smoke constituents, in tobacco products. Topics for discussion include the criteria for selection of the constituents, developing a proposed list of harmful or potentially harmful constituents, the rationale for including each constituent, and the acceptable analytical methods for assessing the quantity of each constituent.”

On August 30, 2010, a meeting of the TPSAC was held at which the TPSAC received a report from the Constituents Subcommittee and was to “discuss a proposed initial list of harmful or potentially harmful constituents, the rationale for inclusion of each constituent, established analytical methods as well as the ancillary methods and normalization standards for the identified constituents.”

Lorillard Tobacco Company (Lorillard) submitted written comments in advance of the June 8-9, 2010 meeting of the Constituents Subcommittee and the August 30, 2010 meeting of the TPSAC. These submissions are or will be available at [www.fda.gov](http://www.fda.gov).

Lorillard presents information below regarding the Draft Guidance to assist FDA in its evaluation, based on sound scientific considerations, of the constituents to be categorized as “harmful and potentially harmful constituents ... to health.”

## **BACKGROUND**

In the Draft Guidance under the heading “Discussion,” FDA-CTP stated:

For the purpose of establishing "a list of harmful and potentially harmful constituents, including smoke constituents, to health in each tobacco product by brand and by quantity in each brand and subbrand," as required under section 904( e) of the Act, FDA believes that the phrase "harmful and potentially harmful constituent" includes any chemical or chemical compound in a tobacco product or in tobacco smoke:

- a) that is or potentially is inhaled, ingested, or absorbed into the body; and
- b) that causes or has the potential to cause direct or indirect harm to users or non-users of tobacco products. Examples of constituents that have the "potential to cause direct harm" to users or non-users of tobacco products include constituents that are toxicants, carcinogens, and addictive chemicals and chemical compounds. Examples of constituents that have the "potential to cause indirect harm" to users or non-users of tobacco products include constituents that may increase the exposure to the harmful effects of a tobacco product constituent by: 1) potentially facilitating initiation of the use of tobacco products; 2) potentially impeding cessation of the use of tobacco products; or 3) potentially increasing the intensity of tobacco product use (e.g., frequency of use, amount consumed, depth of inhalation). Another example of a constituent that has the "potential to cause indirect harm" is a constituent that may enhance the harmful effects of a tobacco product constituent.

## **DRAFT GUIDANCE**

### **A. “Harmful and Potentially Harmful Constituents” should not include constituents that are deemed to cause or to have the potential to cause “indirect harm”**

The Draft Guidance broadens the scope of “harmful and potentially harmful constituents” to include constituents “that causes or have the potential to cause indirect harm.” In Section 904(e) the FDA is required only to establish “a list of harmful and potentially harmful constituents, including smoke constituents, to health...” There is presently no scientific method available to measure any “indirect harm” from any tobacco or tobacco smoke constituent, as “indirect harm” is defined in the Draft Guidance.

As pointed out in the comments of Philip Morris USA Inc. and U.S. Smokeless Tobacco Company LLC, filed on August 23, 2010, the language used by Congress in Section 904(e) is not as broad as the language used in other sections of the Act. For example, Section 904(a)(4) states that the following information shall be provided to the Secretary:

Beginning 6 months after the date of enactment of the Family Smoking Prevention and Tobacco Control Act, all documents developed after such date of enactment that relate to

health, toxicological, behavioral, or physiological effects of current or future tobacco products, their constituents (including smoke constituents), ingredients, components, and additives [emphasis added].

Comparing the language of Sections 904(a)(4) and 904(e), Congress apparently did not intend to include constituents which relate to the indirect harm of behavioral effects in its mandate to the Secretary to develop “a list of harmful and potentially harmful constituents, including smoke constituents, to health...” A similar comparison can be made between the language of Sections 907(a)(3)(B)(1), 910(c)(4) and 904(e). Section 907(a)(3)(B)(1), relating to tobacco product standards, and Section 910(c)(4), relating to certain new tobacco products, both contemplate an assessment of certain behavioral effects of products, including “the increased or decreased likelihood that existing users of tobacco products will stop using such products” and “the increase or decreased likelihood that those who do not use tobacco products will start using such products.” The absence of any such language in Section 904(e) relating to smoking cessation, initiation or other behavioral effects, indicates that Congress did not intend for these issues to be considered in connection with Section 904(e). Instead, Section 904(e) should relate only to the direct harm or potential harm of constituents to health and the Draft Guidance should be revised accordingly.

**B. The term “constituents” should not include additives or ingredients added to tobacco, which are fully considered and covered specifically by other provisions of the Act.**

Although the Act does not contain a definition of “constituent,” Section 900(17) of the Act defines “Smoke constituent” as: “Any chemical or chemical compound in mainstream or sidestream tobacco smoke that either transfers from any component of the cigarette to the smoke or that is formed by the combustion or heating of tobacco, additives, or other component of the tobacco product.” The Act clearly anticipates that this definition does not include additives, which are defined separately in Section 901(1) as:

[a]ny substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristic of any tobacco product (including any substance intended for use as a flavoring or coloring or in producing, manufacturing, packing, processing, preparing, treating, packing, transporting, or holding), except that such term does not include tobacco or a pesticide chemical residue in or on raw tobacco or a pesticide chemical.

Despite these definitions, two additives (coumarin and eugenol) were included on the initial recommended list presented by the Constituents Subcommittee to the TPSAC. The Act has specific provisions dealing with ingredients and additives, quite separate and distinct from the charge to the Secretary to develop a list of “harmful and potentially harmful constituents, including smoke constituents, to health” (*See, e.g.*, Sections 904(a)(1), 904(a)(4),

907(a)(3)(B)(ii) and 915(b)(1)). Tobacco product ingredients and additives are fully considered and comprehensively reported under other provisions of the Act.

In addition, studies of the smoke composition of cigarettes with and without added ingredients have shown that the addition of ingredients to cigarettes does not alter the composition of cigarette smoke appreciably (Rodgman (2002), Carmines (2002), Rustemeier *et al.* (2002), Baker and Bishop (2004), Paschke *et al.* (2002)). More importantly, numerous studies have shown that the addition of ingredients to cigarettes does not increase the biological activity or toxicity of the smoke from those cigarettes. (Paschke *et al.* (2002), Rodgman (2002), Roemer *et al.* (2002), Gaworski *et al.* (1997), Gaworski *et al.* (1999), Vanscheeuwijck *et al.*, 2002)).

**C. Any evaluation of “harmful and potentially harmful constituents, including smoking constituents, to health” should consider whether the constituents are “harmful or potentially harmful” to health at the level present in tobacco smoke and whether such level can be measured reliably.**

Cigarette smoke is a complex, dynamic and reactive mixture of chemical constituents. Hundreds of scientific publications have examined the constituents in cigarette smoke (*See, e.g.*, Hoffmann (1993), Borgerding and Klus (2005), Rodgman and Perfetti (2009)). Over 8,000 chemical constituents have been identified in cigarette smoke to date (Rodgman and Perfetti (2009)).

Over 50 years of research have been devoted to the identification of constituents of tobacco and smoke, and contemporary analytical chemistry methods have accounted for thousands of individual compounds, elements, permanent gases and pyrolysis/combustion products of variable composition. The biological activity of these smoke constituents (both individual compounds and compound classes) ranges from toxic and carcinogenic to anti-carcinogenic and benign. Dozens, or perhaps hundreds, of the currently identified constituents of tobacco smoke are known or suspected to possess toxic properties at some level of exposure or dose. Relatively fewer are found in tobacco and tobacco smoke at levels that may be plausibly hypothesized to play a role in the etiology of major tobacco-related diseases.

Indeed, it is axiomatic that all substances have the potential to induce toxicity at some sufficiently high level of exposure or dose. At some extreme level of exposure or dose, any of the 8,000 constituents identified in tobacco smoke, including water, could be “harmful.” Further, under the broadest definition, any of these constituents could be claimed to be “potentially harmful” due to their mere presence in tobacco smoke. An expansion of the phrase “harmful or potentially harmful” to this extent cannot be what Congress intended because it would have no regulatory efficacy. Every contemporary regulatory regime intended to address and control the health risks to individuals or to populations that may result from exposures to substances in the

diet, the workplace or the environment includes consideration of the magnitude of exposure to the substances of interest. Any categorization of a constituent in tobacco or tobacco smoke as “harmful or potentially harmful ... to health” should be founded on sound, contemporary scientific principles which must take into consideration the level of exposure to the constituent that occurs consequent to tobacco use.

The Draft Guidance, however, does not address the appropriate scientific method or basis necessary to narrow the application of this phrase. Any evaluation of “harmful or potentially harmful constituents, including smoke constituents, to health” should be based on the strength of the evidence for each constituent as a contributor to disease risks under the conditions of exposure that accompany tobacco use. This requires a rigorous evaluation of all scientific evidence related to the constituent. For example, several of the lists of constituents provided to the Constituents Subcommittee and the TPSAC include a number of constituents that are neither notably toxic in exposure levels resulting from tobacco use, nor carcinogenic at any level (*e.g.* acetone, ammonia, ammonium ion, anabasine, selenium, pyridine, eugenol, nitrate, normicotine, and toluene). The purported harmful effects of some of these provisionally-listed constituents were discussed in the context of extremely high levels of experimental dosing or industrial overexposures that greatly exceed those that could plausibly result from tobacco products.

This evaluation should also include a critical assessment of the reliability of method used to measure the presence and amount of the constituent in tobacco and tobacco smoke. A standardized analytical chemistry method of analysis for each constituent that is sufficiently robust, reproducible and validated should be required in order to reliably quantify the level of the constituent in tobacco and tobacco smoke.

The Draft Guidance simply does not incorporate a process that ensures that a constituent in tobacco or tobacco smoke is categorized as “harmful or potentially harmful ... to health” based on sound science.

## CONCLUSION

Lorillard offers these comments regarding the Draft Guidance to assist FDA in its evaluation of the tobacco and tobacco smoke constituents to be categorized as “harmful and potentially harmful constituents, including smoke constituents, to health.” Lorillard believes that this evaluation should be based on sound science.

- Any such categorization should not include constituents that are deemed to cause or to have the potential to cause “indirect harm.”
- The definition of “constituents” in the Draft Guidance should not be expanded beyond the language of the Act by including additives or ingredients added to tobacco.
- A rigorous evaluation of all scientific evidence related to a constituent should be undertaken and any categorization of a constituent as “harmful or potentially harmful” should be based on the strength of the evidence for the constituent as a contributor to disease risks at the level found in tobacco or tobacco smoke. This evaluation should also include a critical assessment of the reliability of method used to measure the presence and amount of the constituent in tobacco and tobacco smoke.

Lorillard believes that the Draft Guidance should be revised to address each of these issues.

Respectfully submitted,



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