



American Heart Association
Learn and Live



October 11, 2011

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2011-N-0271

To Whom It May Concern:

The Campaign for Tobacco-Free Kids, the American Cancer Society Cancer Action Network, the American Heart Association, the American Legacy Foundation, and the American Lung Association submit these comments in the above-designated docket.

Section 904(e) of the Tobacco Control Act requires FDA to establish and periodically revise as appropriate “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.” The first step in this process is the development of a definition of “harmful and potentially harmful constituents.” FDA’s final guidance defines this term to “include 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 cause or has the potential to cause direct or indirect harm to users or non-users of tobacco products.” The guidance makes clear that the term includes not only constituents that are toxicants, carcinogens, or addictive substances, but also constituents that “[1] potentially facilitate initiation of the use of tobacco products; [2] potentially impede[] cessation of the use of tobacco products; or [3] potentially increase[] the intensity of tobacco product use [e.g., frequency or use, amount consumed, depth of inhalation].” The definition also states that it includes “a constituent that may enhance the harmful effects of a tobacco product constituent.” The above-designated notice specifically adheres to this broad definition. The undersigned organizations strongly support the FDA’s continued adherence to this definition. In formulating the definition, FDA properly sought to define what was “harmful or potentially harmful” in terms of the dangers to public health elaborated at several points in the statute (e.g., Section 907(a)(3), Section 910(c)(4), etc.). The incorporation of these standards in the definition of “harmful and potentially harmful constituents” is necessary to give effect to the underlying purpose of the legislation: to protect

and promote the public health, as measured by the effects on both users and nonusers of tobacco products.

FDA appointed a subcommittee of the Tobacco Products Scientific Advisory Committee (“TPSAC”) and charged them with developing a list of harmful and potentially harmful constituents. The Subcommittee developed such a list, and the list was subsequently approved by the TPSAC. This process was appropriate.

From the outset of the Subcommittee’s consideration, it was clear that the list that would be developed would not be complete, but rather would be an “initial list” that would be augmented later. In the initial presentation to the Subcommittee, FDA stated that “the initial list. . .will focus on consideration of substances previously identified as harmful on example lists developed by some countries, the Hoffman analyte list, and the World Health Organization including the International Agency for Research on Cancer.”¹

FDA thus directed the Subcommittee to limit its consideration of constituents to those which met a set of criteria significantly more narrow than the definition of “harmful or potentially harm constituent” that the statute mandates and that the agency itself had adopted. The criteria FDA directed the Subcommittee to use limited the list to substances that were themselves carcinogenic, toxic, or addictive. Moreover, as FDA itself has stated, the list focuses on only five disease outcomes (cancer, cardiovascular disease, respiratory effects, developmental or reproductive effects, and addiction). The FDA notice specifically states that FDA “intends to review other disease outcomes to assess whether additional chemicals or chemical compounds should be added to the list and to consider unspecified “additional criteria” to help identify other constituents that should be listed. The notice states that FDA “will continue to review scientific information about tobacco constituents” both before and after it establishes its list of harmful and potentially harmful constituents pursuant to section 904(e).

FDA’s notice appropriately makes clear that the list of constituents contained in the notice is not exhaustive. FDA specifies three categories of constituents that may be added in the future: those that may not have been adequately studied or systematically reviewed by relevant agencies, those that may contribute to disease outcomes other than the five specified in the notice, and those that may meet “additional criteria.” However, this specification leaves out an additional category: constituents that while not toxic, carcinogenic, or addictive themselves, may nevertheless contribute to the toxicity, carcinogenicity, or addictiveness of one or more tobacco products. For example, pH modifiers and buffering substances that may or may not be harmful or addictive given alone in doses comparable to those provided by the tobacco product may increase the product’s addictiveness and/or harmful exposure levels (e.g., urea and related substances.) We urge FDA to take the necessary take steps to identify such constituents and add them to the list as soon as possible. Moreover, neither the Subcommittee nor the Committee included any constituent on the list unless there was a recognized method for measuring them.² Both the Committee and the Subcommittee recognized that constituents in smokeless tobacco

products were underrepresented on the list because less research had been done on constituents in these products.³

Although it is understandable, given statutory deadlines and the ongoing nature of scientific inquiry, that FDA's initial list of harmful and potentially harmful constituents would not be exhaustive, FDA should attempt to ensure that a procedure is in place to add constituents to the list as soon as information becomes available that would justify amendment of the list. Thus, FDA should identify a group, either within or outside the agency, with specific responsibility for monitoring the scientific literature and meeting regularly to consider and recommend modifications to the list.

Moreover, particularly given the limitations of the list, FDA should make it clear that no one should conclude that the absence of a constituent on the initial list implies that such a constituent is not harmful or potentially harmful and that any representation to the contrary would be at best misleading.

Consideration of specific constituents

Although the list in large part follows the list of harmful or potentially harmful constituents approved by the TPSAC, there are significant departures that cause concern. Comparing the list approved by the TPSAC with the list published in the above-designated notice makes this clear. Many constituents were listed by the TPSAC as falling in several categories (i.e., carcinogen, respiratory toxicant, cardiovascular toxicant, reproductive toxicant, or addictive). In numerous cases, however, even though the constituent was listed in the FDA notice, it was designated as falling in fewer categories than those identified by the TPSAC. There was no explanation for these changes. These discrepancies may have limited consequences because such constituents will still be listed, but an explanation for the discrepancy should be noted.

In addition, several constituents that appeared on the list approved by the TPSAC were excluded from the list published in the notice—again with no explanation. We understand that several experts with well-recognized credentials will be submitting comments raising questions about most or all these exclusions and we base our comments in substantial part on consultation with such experts and with other experts in the field.

The following constituents were identified by TPSAC as harmful or potentially harmful but they did not appear on the list published in the current notice.

Nitric oxide/nitrogen oxides. Data submitted to the Subcommittee stated the following.

Respiratory—Nitrogen oxide causes lung inflammation⁴

Cardiovascular—Exposure to oxidizing gases are a likely chemical cause of ischemic heart disease from tobacco smoke exposure⁵

Reproductive or Developmental—Prenatal exposure to nitrogen dioxide in rats led to decreased ability to perform developmental tasks such as righting reflex, negative geotaxis and air righting.⁶

Moreover, the EPA has recently completed a full review of the research and found nitrogen oxides linked to a wide range of harm to respiratory and cardiovascular health.⁷

Nitrates and Nitrites. Nitrates and nitrites in tobacco lead to the formation of carcinogenic compounds. They are the main precursors of nitrosamines. These materials are limited in drinking water because they cause respiratory problems. In oral tobacco products these compounds react directly with compounds in tobacco. Nitrate plus nicotine produces a key tobacco-specific nitrosamine that is not produced in the absence of the nitrate, nitrite or nitrogen oxides. In tobacco smoke it is the oxides of nitrogen that are important to respiratory toxicity as well as forming the dangerous class of carcinogens, the nitrosamines. The tobacco industry developed technology for the reduction of nitrates in tobacco because they recognized the potential harm of the compounds and the oxides of nitrogen in smoke have long been considered a key toxicant. Materials submitted to the Subcommittee noted numerous authorities that have classified nitrates and nitrites as carcinogens, respiratory toxicants or cardiovascular toxicants.

Nitroanabasine. Data submitted to the Subcommittee stated as follows.

Cancer—The IARC concluded that there is limited evidence of N-nitroanabasine (NAB) carcinogenicity in experimental animals and that NAB was not classifiable as to its carcinogenicity in humans).⁸ NAB is commonly measured with NNN, NNK and NAT.

In light of the fact that the listing under Section 904(e) is to include both harmful and potentially harmful constituents, the evidence concerning nitroanabasine would appear to be sufficient to warrant its inclusion on the list.

Tar. Tar should be included because it is both toxic in itself and a measure of the total mass of the particulate matter in the smoke. Without a measurement of tar, there is no method by which the toxicants on the list can be normalized (i.e., expressed as a quantity of any constituent per milligram of tar) based on the particulate mass of smoke. Numbers expressed only in terms of milligrams per cigarette will be potentially misleading because of the variability of smoke produced in ventilated cigarettes. It is possible to normalize to nicotine, but it is possible to manipulate nicotine independent of the total mass of smoke generated, and thus measurement of tar is essential. The absence of a measurement for tar also makes it more difficult to compare current conditions to a large amount of accumulated historical data. Revising the method of testing for tar is necessary. Also, knowing the relationship of the amount tar to that of nicotine may be useful.

Butyraldehyde. Data submitted to the Subcommittee stated the following:

Respiratory—Butyraldehyde is a volatile aldehyde. Volatile aldehydes are thought to contribute to cigarette smoke-related chronic obstructive lung disease⁹

Cardiovascular—Butyraldehyde causes increased blood pressure in animal studies¹⁰ Aldehydes are proposed to play a role in lipid peroxidation, a contributing factor in vascular disease.^{11 12}

Eugenol. Data submitted to the Subcommittee stated the following:

“Respiratory—Laboratory rats inhaling eugenol displayed dose-related signs of respiratory irritation.¹³ Eugenol, the major active ingredients in cloves, is believed to be the probable cause of the severe lower respiratory complications—acute lung injury and hemorrhage—that occurs in some users of clove cigarettes.¹⁴ Similar effects (congestion of the lung with interstitial hemorrhages, acute emphysema, and acute pulmonary edema) were observed in rats but not hamsters following intratracheal administration of eugenol.”¹⁵

Pyridine. Pyridine is a significant respiratory toxicant with a short term exposure limit on the order of 10 ppm. It has been added to cigarettes during the manufacturing process and is also a known central nervous system pharmacological agent. While it has been used as a food additive, inhalation of pyridine is a definite risk. Data submitted to the Subcommittee stated the following:

Respiratory—Rats inhaling pyridine exhibited adverse respiratory effects described as inhibited lipid formation and decreased protein syntheses and phospholipid content in pneumocytes. The effects increased in severity with exposure with a decline in the phospholipid content in alveolar cells and in the surface-active lining of alveoli after 36 days.¹⁶ Pyridine causes respiratory tract irritation.¹⁷

Resorcinol. Resorcinol is an isomer of catechol and is known to form quinones. The mechanism of catechol carcinogenesis is likely to be similar in resorcinol. This is an interesting case of chemical similarity that simply rates one as a respiratory toxicant while the other is both a respiratory toxicant and a carcinogen. Data submitted to the Subcommittee stated:

Respiratory—Resorcinol is irritating to mucous membranes.¹⁸ Resorcinol is toxic to the ciliated cells in the lung.¹⁹

Publication of the List

Section 904(d) requires the Secretary to publish the list compiled pursuant to Section 904(e). That list will contain an enumeration and quantification of the harmful and potentially harmful constituents in each tobacco product, by brand and subbrand. Section 904(d)(2) requires the Secretary to conduct “periodic consumer research to ensure that the list published under paragraph (1) is not misleading to lay persons.” We urge the FDA to begin to undertake this

research before the list is published for the first time to ensure that the information provided is neither misunderstood nor misused. Such information has a high potential for being used to mislead consumers into believing that one highly dangerous product is somehow less dangerous than another.

Once FDA has studied and understood consumer response to different ways of disclosing the list of harmful and potentially harmful constituents, it is essential that FDA be careful to insure that the disclosure of the list on a brand and sub-brand basis does not mislead consumers about the relative safety of different products or of the different constituents and level of constituents in different products.

In measuring constituents, it is important to measure the actual emissions to which the user might be exposed and not just the contents of the unused product. The act of smoking a cigarette, including the pyrolysis and puffing necessary for the operation of the cigarette and the inhalation of smoke produces emissions that may be new and/or substantially higher than the level of constituents present in the unused product. For example, acetaldehyde may be produced and occur in the emission by the combination of various sugars and other constituents by the pyrolysis and actual operation of the cigarette. The setting of performance standards for maximal levels of such substances should be based on the content of the final emissions as the maximal levels that might occur during actual use of the product.

In addition, no one should conclude that the level of any constituent or set of constituents is the sole determinant of the harmfulness of a tobacco product. The physical design features of drug-delivering formulations can contribute to harmful and addictive effects by altering the dosing characteristics, function and variability exposures. Cigarettes have been intentionally designed over many decades to be “flexible” or “elastic” in their delivery of nicotine and other substances. This potential is part of the basis for recommendations to discontinue publication of FTC cigarette yield information. Physical design features include ventilation holes, selective filter design features, and the size and density of packing of tobacco particles. Physical design features may also alter addictiveness by altering the ratio of unprotonated (aka “free-base” or “unionized”) nicotine to protonated (aka “nicotine salt” or “ionized”) nicotine. Filter ventilation holes are an example of this, as demonstrated by the CDC study by Watson, Trommel and Ashley, 2004.²⁰ Because design features and manufacturing techniques can be relevant in determining the harmfulness of a tobacco product, FDA should consider such elements in future regulatory action.

Sincerely,



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- ¹ Summary Memorandum from the Director, Center for Tobacco Products, to the Subcommittee of May 12, 2010, presented at the Subcommittee meeting on June 8, 2010.
- ² Presentation of Corinne Husten to the TPSAC, August 30, 2011.
- ³ Presentation of Corinne Husten to the TPSAC, August 30, 2011.
- ⁴ Hoffmann, D. and Hoffman, I., "*The Changing Cigarette: Chemical Studies and Bioassays*," Chapter 5, in Risks Associated with Smoking Cigarettes with Low Tar Machine-Yields of Tar and Nicotine, Monograph 13, Department of Health and Human Services, 2001, Washington, D .C.
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- ⁶ Tabacova, S. et al., "Postnatal Effects of Maternal Exposure to Nitrogen Dioxide," *Neurobehav Toxicol Teratol*, Vol. 7, 1985, pp. 785-789.
- ⁷ US Environmental Protection Agency, Integrated Science Assessment for Oxides of Nitrogen. July 2008. EPA/600/R-08/071. Available at <http://cfpub.epa.gov/ncea/cfm/recorddisplay.cfm?deid=194645>.
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- ¹⁷ Hoffmann, D. and Hoffman, I., "*The Changing Cigarette: Chemical Studies and Bioassays*," Chapter 5, in Risks Associated with Smoking Cigarettes with Low Tar Machine-Yields of Tar and Nicotine, Monograph 13, Department of Health and Human Services, 2001, Washington, D .C.
- ¹⁸ States National Library of Medicine (NLM), *Toxicology Data Network (TOXNET)*, Hazardous Substances Database (HSDB). HSDB Database, Resorcinol, (CASRN: 108-46-3), 2010g.
- ¹⁹ Dalhamn, T. and Lagersted, B., "Ciliostatic Effect of Phenol and Resorcinol," *Arch Otolaryngol*, Vol. 84, No. 3, 1966, pp. 325-328.
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