IV. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) either electronic or written comments regarding this document. It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received documents may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

V. Electronic Access

Persons with access to the Internet may obtain an electronic version of this guidance document at *http://www.regulations.gov* and *http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/default.htm*.

Dated: March 23, 2012.

Leslie Kux,

Assistant Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2012–N–0143]

Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Established List

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; establishment of a list.

SUMMARY: The Food and Drug Administration (FDA) is establishing a list of harmful and potentially harmful constituents (HPHCs) in tobacco products and tobacco smoke (the established HPHC list) as required by the Federal Food, Drug, and Cosmetic Act (the FD&C Act).

FOR FURTHER INFORMATION CONTACT: Carol Drew, Center for Tobacco Products, Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850–3229, 877–287–1373.

SUPPLEMENTARY INFORMATION:

I. Introduction

On June 22, 2009, the President signed the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) (Pub. L. 111–31) into law. The Tobacco Control Act amended the FD&C Act (21 U.S.C. 301 *et seq.*) by, among other things, adding a new chapter granting FDA important new authority to regulate the manufacture, marketing, and distribution of tobacco products to protect the public health. Section 904(e) of the FD&C Act (21 U.S.C. 387d(e)), as added by 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 Agency has considered comments solicited from the public, as well as scientific and other information, and has developed a list of tobacco product constituents it currently believes are harmful or potentially harmful to health. We are establishing this list as table 1 of this document as required by section 904(e) of the FD&C Act. In this document, we are also providing information about related actions, including the Agency's guidance discussing the meaning of HPHC, the criteria the Agency used to help develop the established HPHC list, the reasons the Agency may add or remove constituents from the established HPHC list consistent with the directive of section 904(e), and the addition of quantities to the list.

II. Background

On January 31, 2011, FDA announced the availability of a guidance entitled '' 'Harmful and Potentially Harmful Constituents' in Tobacco Products as Used in Section 904(e) of the Federal Food, Drug, and Cosmetic Act'' (76 FR 5387) (available at *www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation*) (HPHC final guidance). This guidance represents the Agency's current thinking on the meaning of the term ''harmful and potentially harmful constituent'' in the context of implementing section 904(e) of the FD&C Act. It states: ''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'' (HPHC final guidance at page 2). The HPHC final guidance includes examples of constituents that have the potential to cause direct harm and examples of constituents that have the potential to cause indirect harm: ''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'' (HPHC final guidance at page 2).

On May 1, 2010, a subcommittee of the Tobacco Products Scientific Advisory Committee (TPSAC),[1] the Tobacco Product Constituents Subcommittee (the subcommittee), was established and charged with making preliminary recommendations to TPSAC on the HPHCs in tobacco products and tobacco smoke. The subcommittee held public meetings on June 8 and 9, 2010, and July 7, 2010. Prior to these meetings, FDA solicited data, information, and/or views on HPHCs in tobacco products and tobacco smoke from the public.[2] At these meetings the subcommittee:

- Reviewed example lists of HPHCs in tobacco products and tobacco smoke developed by other countries and organizations;
- Identified criteria for selecting carcinogens, toxicants, and addictive chemicals or chemical compounds in tobacco products and tobacco smoke;
- Identified chemicals or chemical compounds that met the identified criteria;
- Confirmed the existence of methods for measuring each chemical or chemical compound identified; and
- Identified other potentially important information or criteria for measuring HPHCs in tobacco products or tobacco smoke, such as smoking machine regimens to be used in measuring HPHCs.

[1] Information about TPSAC as well as information and background materials on TPSAC meetings are available at *http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/default.htm*.

[2] See 75 FR 22147 (April 27, 2010) and 75 FR 33814 (June 15, 2010). Information submitted to the public docket for each of these meetings is available at *http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/ucm222977.htm* and *http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/ucm222978.htm*.

The subcommittee made preliminary recommendations to TPSAC.

On August 30, 2010, TPSAC held a public meeting to deliberate on the recommendations from the subcommittee. Prior to this meeting, FDA published a notice in the **Federal Register** soliciting data, information, and/or views from the public on the issues to be discussed at this meeting.[3] FDA asked what criteria TPSAC recommended the Agency use for determining whether a constituent is a carcinogen, toxicant, or addictive chemical or chemical compound that should be included on the established HPHC list. As a result of its discussions, TPSAC recommended to the Agency the following criteria for selecting the established HPHC list:

- Constituents identified as known or probable human carcinogens by either the International Agency for Research on Cancer (IARC), the U.S. Environmental Protection Agency (EPA), or the National Toxicology Program;
- Constituents identified as possible human carcinogens by IARC or EPA and/or identified by the National Institute for Occupational Safety and Health as potential occupational carcinogens;
- Constituents identified by EPA or the Agency for Toxic Substances and Disease Registry (ATSDR) as having adverse respiratory or cardiac effects;
- Constituents identified by the California Environmental Protection Agency as reproductive or developmental toxicants;
- Constituents having, based upon a review of the peer-reviewed literature, evidence of at least two of the following measures of abuse liability (addiction):
  - Central nervous system activity;
  - Animal drug discrimination;
  - Conditioned place preference;
  - Animal self-administration;
  - Human self-administration;
  - Drug liking;
  - Signs of withdrawal; and
- Constituents banned in food (for smokeless tobacco products).

On August 12, 2011, FDA published a notice in the **Federal Register** (76 FR 50226) (the August 12 notice[4]) stating that the Agency had tentatively concluded that it should consider a constituent meeting the criteria listed in that document to be harmful or potentially harmful, such that the constituent should be included on the HPHC list, unless other scientific information obtained by or submitted to the Agency shows that the constituent is not, in fact, harmful or potentially harmful. The August 12 notice also included a list of constituents that was developed by applying this approach to available information and requested that interested persons submit scientific and other information concerning the harmful and potentially harmful constituents in tobacco products and tobacco smoke. The August 12 notice stated that the Agency was particularly interested in comments on the following issues: (1) The criteria FDA should use in determining whether a constituent is harmful or potentially harmful such that it should be included on the established HPHC list; (2) whether any chemicals or chemical compounds not listed should be added because they are harmful or potentially harmful, including supporting scientific or other information; and/or (3) whether any chemicals or chemical compounds should be removed because they are not harmful or potentially harmful, including supporting scientific or other information.

The Agency has considered all of the comments submitted to the docket for the August 12 notice and has reviewed scientific and other information submitted to support these comments. Based on the information before it and its own knowledge and expertise, FDA concludes that it should consider a constituent meeting the criteria proposed in the August 12 notice to be harmful or potentially harmful, such that it should be included on the HPHC list, unless other scientific information obtained by or submitted to the Agency shows that the constituent is not, in fact, harmful or potentially harmful. Applying these criteria, and after consideration of comments and supporting information submitted to the docket for the August 12 notice, FDA has developed the established list of harmful and potentially harmful constituents in tobacco products and tobacco smoke as table 1 of this document.

Three constituents included on the list we published for comment in the August 12 notice are not included in table 1. Based on information submitted to the docket and our review of the scientific literature, we have determined not to include dibenz[a,h]acridine, dibenz[a,j]acridine and 7H-dibenz[c,g]carbazole on the established HPHC list at this time because there is not sufficient evidence that they are found in tobacco products or tobacco smoke. This decision is based on information presently before us, and may be revised, consistent with the directive in section 904(e) of the FD&C Act that FDA periodically revise the established list as appropriate.

We note that certain metals on the established HPHC list (beryllium, cadmium, chromium, cobalt, lead, mercury, nickel, and selenium) may exist in tobacco products and tobacco smoke in the elemental form and/or in compounds. Both the elemental and compound forms are harmful and/or potentially harmful under our criteria. Identification of a metal on the established HPHC list therefore refers to the metal regardless of whether it is found in its elemental form or as a metal-bound compound. For example, beryllium includes both elemental beryllium and beryllium found in beryllium compounds.

FDA recognizes that the established HPHC list may not include all constituents that are ''harmful or potentially harmful.'' For example, several of the criteria described in this document depend on a chemical or chemical compound being both studied and listed by another entity, such as constituents identified by EPA or ATSDR as having adverse respiratory or cardiac effects. The fact that a constituent has not been so identified by EPA or ATSDR could be because it has not been adequately studied or has not yet been systematically reviewed by relevant Agencies, rather than because the constituent does not have adverse respiratory or cardiac effects. Moreover, FDA has only focused on the five disease outcomes of cancer, cardiovascular disease, respiratory effects, developmental or reproductive effects, and addiction. FDA intends to review other disease outcomes to assess whether additional chemicals or chemical compounds in tobacco products or tobacco smoke are harmful or potentially harmful constituents that contribute to the risk of other diseases.

In addition, the criteria FDA has selected are limited to those that relate to carcinogens, toxicants, and addictive chemicals or chemical compounds in tobacco products and tobacco smoke. We intend to consider whether additional criteria should be selected to help identify other classes of harmful or potentially harmful chemicals and chemical compounds for inclusion on the established HPHC list, and whether individual constituents should be added. Just as these types of new information may lead to additions to the established HPHC list, FDA recognizes

[3] See 75 FR 47308 (August 5, 2010). Information submitted by the public to the docket for this meeting is available at *http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/ucm232799.htm*.

[4] ''Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Request for Comments,'' 76 FR 50226 (August 12, 2011).

that it may become aware of new scientific information about constituents of tobacco products that make it appropriate to remove one or more of the constituents that appear on the list. Thus, FDA will continue to review scientific information about tobacco product constituents. For these reasons and consistent with the directive of section 904(e) of the FD&C Act, FDA intends to periodically revise as appropriate the established HPHC list.

Currently, the established HPHC list in table 1 does not contain quantities of the HPHCs by brand and subbrand. Beginning June 22, 2012, sections 904(a)(3) and 904(c)(1) of the FD&C Act require tobacco product manufacturers and importers or their agents to submit a list of constituents, including smoke constituents as applicable, identified by FDA as harmful or potentially harmful to health in each of their tobacco products, by brand and by quantity in each brand and subbrand. Elsewhere in this issue of the **Federal Register**, FDA is publishing a notice announcing the availability of a draft guidance for industry to assist persons reporting to FDA the quantities of harmful and potentially harmful constituents in tobacco products and tobacco smoke. FDA intends to use the data and information submitted under sections 904(a)(3) and 904(c)(1) to, as directed by section 904(d)(1) of the FD&C Act, place on public display the list of HPHCs established under section 904(e), by brand and by quantity in each brand and subbrand, in a format ''that is understandable and not misleading to a lay person.''

TABLE 1—ESTABLISHED LIST OF THE CHEMICALS AND CHEMICAL COMPOUNDS IDENTIFIED BY FDA AS HARMFUL AND POTENTIALLY HARMFUL CONSTITUENTS IN TOBACCO PRODUCTS AND TOBACCO SMOKE

Constituent	Carcinogen (CA), respiratory toxicant (RT), cardiovascular toxicant (CT), reproductive or developmental toxicant (RDT), addictive (AD)
Acetaldehyde	CA, RT, AD
Acetamide	CA
Acetone	RT
Acrolein	RT, CT
Acrylamide	CA
Acrylonitrile	CA, RT
Aflatoxin B1	CA
4-Aminobiphenyl	CA
1-Aminonaphthalene	CA
2-Aminonaphthalene	CA
Ammonia	RT
Anabasine	AD
o-Anisidine	CA
Arsenic	CA, CT, RDT
A-α-C (2-Amino-9*H*-pyrido[2,3-*b*]indole)	CA
Benz[*a*]anthracene	CA, CT
Benz[*j*]aceanthrylene	CA
Benzene	CA, CT, RDT
Benzo[*b*]fluoranthene	CA, CT
Benzo[*k*]fluoranthene	CA, CT
Benzo[*b*]furan	CA
Benzo[*a*]pyrene	CA
Benzo[*c*]phenanthrene	CA
Beryllium	CA
1,3-Butadiene	CA, RT, RDT
Cadmium	CA, RT, RDT
Caffeic acid	CA
Carbon monoxide	RDT
Catechol	CA
Chlorinated dioxins/furans	CA, RDT
Chromium	CA, RT, RDT
Chrysene	CA, CT
Cobalt	CA, CT
Coumarin	Banned in food
Cresols (o-, m-, and p-cresol)	CA, RT
Crotonaldehyde	CA
Cyclopenta[*c,d*]pyrene	CA
Dibenz[*a,h*]anthracene	CA
Dibenzo[*a,e*]pyrene	CA
Dibenzo[*a,h*]pyrene	CA
Dibenzo[*a,i*]pyrene	CA
Dibenzo[*a,l*]pyrene	CA
2,6-Dimethylaniline	CA
Ethyl carbamate (urethane)	CA, RDT
Ethylbenzene	CA
Ethylene oxide	CA, RT, RDT
Formaldehyde	CA, RT
Furan	CA
Glu-P-1 (2-Amino-6-methyldipyrido[1,2-*a*:3',2'-*d*]imidazole)	CA

TABLE 1—ESTABLISHED LIST OF THE CHEMICALS AND CHEMICAL COMPOUNDS IDENTIFIED BY FDA AS HARMFUL AND POTENTIALLY HARMFUL CONSTITUENTS IN TOBACCO PRODUCTS AND TOBACCO SMOKE—Continued

Constituent	Carcinogen (CA), respiratory toxicant (RT), cardiovascular toxicant (CT), reproductive or developmental toxicant (RDT), addictive (AD)
Glu-P-2 (2-Aminodipyrido[1,2-*a*:3',2'-*d*]imidazole)	CA
Hydrazine	CA, RT
Hydrogen cyanide	RT, CT
Indeno[*1,2,3-cd*]pyrene	CA
IQ (2-Amino-3-methylimidazo[4,5-*f*]quinoline)	CA
Isoprene	CA
Lead	CA, CT, RDT
MeA-α-C (2-Amino-3-methyl)-9*H*-pyrido[2,3-*b*]indole)	CA
Mercury	CA, RDT
Methyl ethyl ketone	RT
5-Methylchrysene	CA
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	CA
Naphthalene	CA, RT
Nickel	CA, RT
Nicotine	RDT, AD
Nitrobenzene	CA, RT, RDT
Nitromethane	CA
2-Nitropropane	CA
N-Nitrosodiethanolamine (NDELA)	CA
N-Nitrosodiethylamine	CA
N-Nitrosodimethylamine (NDMA)	CA
N-Nitrosomethylethylamine	CA
N-Nitrosomorpholine (NMOR)	CA
N-Nitrosonornicotine (NNN)	CA
N-Nitrosopiperidine (NPIP)	CA
N-Nitrosopyrrolidine (NPYR)	CA
N-Nitrososarcosine (NSAR)	CA
Nornicotine	AD
Phenol	RT, CT
PhIP (2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine)	CA
Polonium-210	CA
Propionaldehyde	RT, CT
Propylene oxide	CA, RT
Quinoline	CA
Selenium	RT
Styrene	CA
o-Toluidine	CA
Toluene	RT, RDT
Trp-P-1 (3-Amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole)	CA
Trp-P-2 (1-Methyl-3-amino-5*H*-pyrido[4,3-*b*]indole)	CA
Uranium-235	CA, RT
Uranium-238	CA, RT
Vinyl acetate	CA, RT
Vinyl chloride	CA

Dated: March 23, 2012.

Leslie Kux,

Assistant Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2012–N–0001]

Peripheral and Central Nervous System Drugs Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: Peripheral and Central Nervous System Drugs Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the Agency on FDA's regulatory issues.

Date and Time: The meeting will be held on May 24, 2012, from 8:30 a.m. to 5 p.m.

Location: FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), 10903 New Hampshire Ave., Silver Spring, MD 20993–0002. Information regarding