August 11, 2015

Food and Drug Administration (FDA)
Office of the Ombudsman
10903 New Hampshire Avenue
WO Building 32, Room 4260
Silver Spring, Maryland 20993

Re: Information Quality Request for Correction

To Whom It May Concern:

I.   A detailed description of the specific material that needs to be corrected including where the material is located.

Chang, et al., "Systemic Review of Cigar Smoking and All Cause and Smoking Related Mortality." *BMC Public Health* 15:390, 2015. Available at http://www.biomedcentral.com/1471-2458/15/390, as promulgated by the Food and Drug Administration in the following instances:
http://www.accessdata.fda.gov/scripts/publications/search_result_record.cfm?id=51907
http://www.fda.gov/TobaccoProducts/NewsEvents/ucm452100.htm

A.   Specific reasons for believing the information does not comply with OMB, HHS, or agency-specific guidelines and is in error and supporting documentation, if any.

1.   The IQA Standards

a. The paper fails to meet HHS's own objectivity standards.

The Information Quality Act (IQA), and IQA guidelines promulgated by the Office of Management and Budget (OMB) and the Department of Health and Human Services (HHS) explain the standards of quality for disseminations of agency information. Among other things, such disseminations must meet the standard of "objectivity." Under the HHS Guidelines:

"Objectivity" involves two distinct elements, presentation and substance. "Objectivity" includes whether disseminated information is being presented in an accurate, clear, complete, and unbiased manner. This involves whether the information is presented within a proper context. Sometimes, in disseminating certain types of information to the public, other information must also be disseminated in order to ensure an accurate, clear, complete, and unbiased presentation. Also, the agency needs to identify the sources of the disseminated information (to the extent possible, consistent with confidentiality protections), and, in a scientific, financial, or statistical context, the supporting data and models, so that the public can assess for itself whether there may be some reason to question the objectivity of the sources. Where appropriate, data should have full, accurate,

transparent documentation, and error sources affecting data quality should be identified and disclosed to users.

The Chang article fails to meet these standards of objectivity. The paper contains inaccuracies, selective reading of the relevant literature, and conclusive statements that cannot be justified by the data. The Food and Drug Administration (FDA) should withdraw the paper to correct these flaws and should not use this article as the basis for regulatory policy.

2.   Examples of IQA Quality Defects in the article

b.   The article's Abstract is inaccurate and not supported by the data.

The Abstract of the paper is inaccurate, concluding that that *"Mortality risks from cigar smoking ... can be as high as or exceed those of cigarette smoking."* In fact, of the ten odds ratios (seven studies) presented in Table 2 on all-cause mortality for *"current cigar"*, only six are statistically significant and none have an odds ratio greater than 1.8; the average lower confidence limit is less than one. Of the ten odds ratios (six studies) presented for *"current cigar and/or pipe,"* only five are statistically significant and none have an odds ratio greater than 1.68; the average lower confidence limit is less than one. By contrast, the FDA (Rostron, 2013) considers that the relative risk of lung cancer in current cigarette smokers is 23.3 (data from CPS-II).

The Abstract also states that *"among primary cigar smokers reporting no inhalation, relative mortality risk was still highly elevated for oral, esophageal, and laryngeal cancers."* These selected statistics consisted of an average of 16, 14, and 6 subjects per study and included several associations that were not statistically significant. Numbers of subjects as low as these cannot be used scientifically to form viable public health positions, especially when they are associated with largely unknown exposures (see below).

Such low confidence and conflicting data cannot fairly be summarized as definitively showing that *"Mortality risks from cigar smoking... can be as high as or exceed those of cigarette smoking."*

c.   The article conflates cigar smokers and other types of tobacco users.

The paper is also inaccurate because it is scientifically incorrect to combine risks derived from several different types of exposures (cigars, pipes, cigarettes) and use that single risk as if it were the risk from one exposure type (cigars). Many cigar smokers used to be cigarette smokers, and as a result of this they have cumulative disease risks that are much higher than those in non-smokers or in exclusive cigar smokers. It is impossible to determine "cigar-only" disease risk in these populations, so that the second half of the paper's Table 2 on all-cause mortality in *"current cigar and/or pipe"* is meaningless. Many cigarette smokers who switch to cigars continue to inhale, unlike most primary cigar smokers. There are thus a variety of types of exposures,

presumably with a variety of effects on disease risk, so that overall conclusions are likely to be erroneous.

A typical set of data from Monograph 9 is reproduced here, for the association between cigar smoking and oral cancer. Data are broadly representative for the other Tables presented in both the Monograph and those copied into the paper. It is clear that for the lowest level of "primary" cigar smoking that there is no increase in risk for oral cancer when compared with never smokers: The odds ratio is 2.2 and the 95% confidence limits are 0.43 and 6.18. Most cigar smokers are very unlikely to smoke more than 2 cigars per day. This fact is noted in the Monograph, where it is stated that "*most cigarette smokers smoke every day. In contrast, as many as three-quarters of cigar smokers smoke only occasionally, and some may only smoke a few cigars per year." This difference in frequency of exposure translates into lower disease risks.*" Tobacco use and alcohol consumption are well known to be synergistic for end-points such as oral cancer (Zeka et al., 2003), a consideration ignored in the paper. The corresponding risks for oral cancer for the lowest level of cigarette smoking are much higher than those reported for cigars, not supporting the statement referenced above "*Mortality risks from cigar smoking... can be as high as or exceed those of cigarette smoking.*"

Rate ratio of buccal and pharyngeal cancer combined by level of cigars/cigarettes per day*

Daily Use	Age (years)				Combined (95% CI)	Deaths**
	35-49	50-64	65-79	80+		
PRIMARY CIGAR						25/18
1-2			2.33		2.12 (0.43,6.18)	
3-4		7.06	6.56		8.51 (3.66,16.77)	
5 +		10.54	15.50		15.94 (8.71,26.75)	
Combined		5.33	7.37		7.92 (5.12,11.69)	
SECONDARY CIGAR						8/18
1-2					4.39 (0.06,24.45)	
3-4						
5 +		5.23	19.62		13.73 (5.50,28.30)	
Combined		1.85	6.89		6.58 (2.83,12.97)	
CIGAR & CIGARETTE						17/18
1-19		9.16	6.93		7.29 (2.66,15.86)	
20		12.00	15.41		13.42 (5.78,26.44)	
21 +			39.04		23.86 (4.80,69.71)	
Combined		8.32	13.01		10.72 (6.24,17.17)	
CIGARETTE ONLY						216/18
1-19		5.98	4.99		5.93 (4.28, 8.02)	
20		10.74	4.34		6.85 (5.37, 8.62)	
21 +		13.41	12.21		12.04 (9.81,14.63)	
Combined		10.52	6.49		8.23 (7.17, 9.40)	

Based on data from CPS-I study. Age-standardized rate ratio for smoking group compared to neversmokers.
* Includes: lip, tongue, floor of mouth, other parts of mouth, mouth unspecified, oral mesopharynx, nasopharynx, hypopharynx, pharynx unspecified, not including salivary glands.
** Number of deaths in subject group/neversmoker group.

      d.   The article relies on research of insufficient sample sizes from which to draw conclusions.

The Abstract of the paper is misleading, since it does not mention the fact that, unlike published epidemiologic studies with cigarettes, the studies for cigars contain on average a very small number of cases (often less than 50) for individual diseases. The sample sizes for cigar smokers are so small that no valid epidemiological data can be drawn from them. Small sample sizes usually produce large confidence intervals, rendering overall interpretation extremely difficult.

In the example given above for oral cancer, there were only 25 cigar smoker deaths in the CPS-1 study, involving more than a million (largely white and well-educated) men and, to a much lesser extent, women) followed from 1959 to 1965 (Thun and Heath, 1997). Data from CPS-II (1.2 million men and women, 1982-1994) also show small numbers of deaths associated with the use of cigars (Shapiro et al., 2000). The subjects of these two large but old studies are not representative of cigar smokers today. These small numbers have led researchers to combine multiple diseases into an epidemiological endpoint termed "all-cause mortality" (see below), to produce larger numbers of cases.

A typical set of data from the CPS-II study is reproduced below, involving 3,541 men who said upon interview in 1982 that they smoked 1-2 cigars per day, and 3,945 men who said that they smoked more than 3 cigars per day. Of the total of 7,486 cigar smokers, a total of 5,063 (68%) claimed subjectively that they did not inhale (see below). For lung cancer there were only 10 deaths in smokers of 1-2 cigars per day, compared with 289 in never smokers. Clearly, the data does not support claims of increased risk for persons smoking cigars at this frequency. The Chang paper glosses over this fact. For all of the other cancer endpoints, there were less than 10 cases in such cigar smokers.

Table 3. Mortality rate ratios and 95% confidence intervals for tobacco-related cancers comparing men who smoked only cigars with men who never smoked, by cigars per day, inhalation, and duration, American Cancer Society's Cancer Prevention Study II (1982 through 1994)*

Cigar smoking status at baseline	Cancer					
	Lung	Oral cavity/pharynx	Larynx	Esophagus	Pancreas	Bladder
Never smokers†						
Rate ratio (95% CI)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
No. of deaths	269	20	5	67	327	94
Current smokers						
Cigars/day						
1–2 cigars/day‡	1.3 (0.7–2.4)	0	6.0 (0.7–53.5)	1.8 (0.6–5.0)	0.6 (0.3–1.4)	0
No. of deaths	10	0	1	4	6	0
≥3 cigars/day§	7.8 (5.9–10.3)	7.6 (2.9–19.6)	15.0 (3.4–65.9)	1.9 (0.8–4.9)	1.6 (1.0–2.5)	1.9 (0.8–4.4)
No. of deaths	68	6	3	5	18	6
Inhalation¶						
No inhalation§	3.3 (2.3–4.7)	3.2 (0.9–11.0)	4.2 (0.5–37.1)	1.6 (0.7–4.1)	0.9 (0.5–1.5)	0.5 (0.1–2.1)
No. of deaths	36	3	1	5	12	2
Inhalation#	11.3 (7.9–16.1)	6.5 (1.4–29.2)	39.0 (8.4–180.1)	1.0 (0.1–7.2)	2.7 (1.5–4.8)	3.6 (1.3–9.9)
No. of deaths	37	2	3	1	12	4
Duration						
<25 y**	2.1 (1.0–4.2)	0	0	0.9 (0.1–6.4)	1.5 (0.7–3.3)	0
No. of deaths	8	0	0	1	7	0
≥25 y††	5.9 (4.5–7.7)	4.6 (1.6–13.0)	13.7 (3.4–54.5)	2.2 (1.0–4.7)	1.1 (0.7–1.8)	1.1 (0.4–2.7)
No. of deaths	75	5	4	8	19	5

Low numbers of deaths associated with cigar smoking are also present in a more modern study. A total of 521,457 subjects were followed from 1991 to 1998 in ten European countries (McCormack et al., 2010). Among never smokers there were a total of 620 "tobacco-related" cancers, compared with 42 cases in exclusive cigar smokers (who said that they never smoked cigarettes). The resulting odds ratio (1.3) is not statistically significant ($p>0.05$): there is no difference between exclusive cigar smokers and never smokers. For lung cancer only, there were 520 cases in exclusive cigarette smokers, 22 in never smokers, and 3 in exclusive cigar smokers. The odds ratio (2.4) is again not statistically significant. Of the seven studies presented in Table 2 on all-cause mortality for "*current cigar*," the average number of cases is 776. Of the six studies presented for "*current cigar and/or pipe*," the average number of cases is 194. Smaller epidemiologic studies are proportionally much more prone to errors due to confounding (particularly by alcohol consumption, as mentioned above) and other factors. Statistical significance of an association between an exposure and a disease outcome is an essential aspect of public health epidemiology.

    e.   The article ignores data on inhalation patterns for premium cigars.

The paper is inaccurate, because it only superficially considers inhalation patterns. The data in the Monograph show minimal all-cause mortality risks (not statistically significant) for low

daily consumption of cigars when compared with non-smokers, an effect almost certainly due to lack of inhalation. The 1998 report referenced above highlights the difference in inhalation patterns between cigarettes and cigars: *"reduction in inhalation is one of the reasons form the difference in disease risks between cigarette and cigar smokers"* (National Cancer Institute, 1998). Less than 5% of cigar smokers were reported to inhale *"moderately"* or *"deeply."* Recent, high-quality papers using biomarkers to clearly demonstrate this lack of inhalation (Funck-Brentano et al., 2006; Rodriguez et al., 2010) were not included in the review.

The statement made that *"smoke particles are deposited in the lung"* is incorrect. The paper that is cited on lung deposition of cigar particles (McDonald et al., 2002) is unconvincing because of its small size and the fact that the findings have not been replicated. Radio-labelled studies often have the failing that the label and the particle of interest often become separated, and this was undoubtedly the case here because they were never associated with each other. In this particular study the articles were not labelled with the tracer: there was a mixed exposure of cigar smoke and the marker, generated from two different sources. Biomarkers such as those referenced above are a much more rigorous way to determine if inhalation had occurred. Thus, blood and/or urine samples can give a much more accurate estimate of the level of inhalation, compared with the highly subjective estimates given by smokers.

      f.   The article is selective in its references to existing data.

The paper is selective, in that not all published work on the subject matter is included (Iribarren et al., 1999). This missing paper reported a range of cardiovascular and other endpoints, compared with most of the studies examined so far where cancer was the endpoint. Key limitations of the missing paper including small sample size, and statistically insignificant associations, are similar to those discussed above, but additional endpoints relating to cardiovascular disease as well as to chronic obstructive pulmonary disease were included. A summary of the data in this paper is presented below. Statistical significance is only present (and then only marginally) for one of the 9 disease sets in consumers of less than 5 cigars per day. Again, these data support the idea that exposure is a major factor mortality and morbidity risk. Instead of grappling with that fact, Chang treats all exposure as equally risky, which is not supported.

TABLE 4. MULTIVARIATE-ADJUSTED RISK OF CARDIOVASCULAR DISEASES, COPD, AND CANCER IN RELATION TO THE AMOUNT OF CIGAR SMOKING AMONG 17,774 MEN.*

OUTCOME	<5 Cigars per Day (N=1177)			≥5 Cigars per Day (N=263)		
	NO. OF EVENTS	RELATIVE RISK (95% CI)	P VALUE	NO. OF EVENTS	RELATIVE RISK (95% CI)	P VALUE
Coronary heart disease	182	1.20 (1.03–1.40)	0.02	62	1.56 (1.21–2.01)	<0.001
Ischemic stroke	58	1.02 (0.78–1.34)	0.88	24	1.29 (0.85–1.94)	0.23
Peripheral arterial disease	15	1.09 (0.64–1.86)	0.73	9	2.17 (1.09–4.32)	0.02
COPD and related conditions	39	1.30 (0.93–1.81)	0.12	18	2.25 (1.39–3.65)	0.001
Oropharyngeal cancer	3	1.34 (0.41–4.42)	0.63	4	7.20 (2.44–21.2)	<0.001
Cancers of the upper aerodigestive tract†	4	1.12 (0.40–3.12)	0.84	5	5.20 (2.00–13.5)	<0.001
Lung cancer	6	1.57 (0.67–3.66)	0.30	3	3.24 (1.01–10.4)	0.04
All smoking-related cancers‡	25	1.17 (0.77–1.77)	0.46	12	2.26 (1.26–4.07)	0.01
All cancers (except non-melanoma skin cancer)	155	1.11 (0.94–1.31)	0.22	33	0.98 (0.69–1.38)	0.89

*Adjustment factors for the calculation of multivariate risks are given in the Methods section. The reference group is men who did not smoke cigars (n=16,228). In 106 men, the amount of cigar smoking was unknown. CI denotes confidence interval.

†Cancers of the upper aerodigestive tract comprised cancers of the oropharynx, nose, larynx, and esophagus.

‡Smoking-related cancers comprised cancers of the upper aerodigestive tract, lung, pancreas, kidney, and bladder.

Specific recommendations for correcting the information.

The Chang article should be withdrawn and HHS should not use it as the basis of regulatory policy. To the extent that HHS believes the article can be corrected, it should at least reflect these two points: (1) there is no evidence to suggest that cigar smokers who smoke 1-2 cigars per day are at increased risk of any disease; and, (2) inhalation of cigar smoke (or the lack thereof), has a direct effect on risk. If HHS has definitive evidence to the contrary, the source of that data must be stated and scrutinized under the IQA.

A description of how the person submitting the complaint is affected by the information error.

Cigar Rights of America (CRA) serves as the sole voice of premium cigar consumers in the United States of America on matters of legislative and regulatory concern, with a membership that spans all 50 states. In addition, CRA members also include professional retail tobacconists that dot "Main Street America," and serve as an historic and social component of the community fabric for those who enjoy premium cigars. However, the cornerstone of CRA is that it is the largest

preeminent coalition of premium cigar manufacturers in the world, with representation of over 60 diverse artisan producers of hand-made premium cigars. This coalition ranges from those that conduct business on an international scale, to the single proprietorship craftsman, who simply wants to produce great hand-made premium cigars. The coalition also includes the entire spectrum of the supply chain, including distributors, growers, mail-order houses, logistics, and associated supporting enterprises. The manufacturer members of CRA are predominantly family owned and entrepreneurial small businesses, built upon the skills that have often been passed down from generation to generation.

These premium cigar manufacturers are likely to be harmed by this dissemination of information if FDA opts to base regulatory policy on its inaccuracies.

Sincerely,

/S/

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