

February 16, 2011

Commissioner Margaret Hamburg, M.D.  
U.S. Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Dear Commissioner Hamburg:

The undersigned individuals are scientists who have considerable experience in conducting or analyzing carcinogenicity studies in animals. We are writing to support a citizen's petition filed by the Center for Science in the Public Interest that calls for the Food and Drug Administration to bar the use of caramel colorings made using an ammonia or ammonia-sulfite process that results in cancer-causing imidazole compounds.

The U.S. National Toxicology Program (NTP) has conducted two-year feeding studies that demonstrated that 4-methylimidazole (4-MI) causes lung tumors in male and female mice and mononuclear cell leukemia in female rats.<sup>1</sup> Other NTP studies found that 2-methylimidazole caused liver tumors in male and female mice, thyroid tumors in male mice, and precancerous thyroid changes in female mice. In rats, 4-MI caused an increased rate of tumors in thyroid follicular cells in females and an increased rate of hyperplasia in thyroid follicular cells in males.<sup>2</sup> The NTP concluded that there is "clear evidence" for carcinogenicity of both chemicals.

4-MI is a potent enough carcinogen that the State of California's Office of Environmental Health Hazard Assessment (OEHHA) is conducting a rulemaking that may result in a requirement that products that expose people to more than 16 micrograms (ug) per day bear a "Proposition 65" cancer warning notice. That level of carcinogen is the amount that could cause, as estimated by OEHHA's methodology, one cancer in 100,000 people, or 3,000 cancers in the American population of some 300 million. A 12-ounce can of popular cola beverages contains in excess of 100 ug, or six times as much as the 16-ug daily limit, indicating the substantially higher risk incurred by regular drinkers of sugar-sweetened and diet colas.

The food industry might contend that negative tumor trends observed in the NTP rat study demonstrate that 4-MI is an anti-carcinogen. We and the OEHHA reject that contention. NTP studies are designed to identify potential carcinogens and not anti-carcinogens. Much of the decreased tumor incidences were likely due to decreased body weight, and, without any knowledge of the mechanism of tumor prevention, it is possible,

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<sup>1</sup> Chan PC, Hills GD, Kissling GE. Toxicity and carcinogenicity studies of 4-methylimidazole in F344/N rats and B6C3F1 mice. Arch Toxicol. 2008;82(1):45-53. (full report at [http://ntp.niehs.nih.gov/files/535\\_Web\\_Final.pdf](http://ntp.niehs.nih.gov/files/535_Web_Final.pdf))

<sup>2</sup> Chan PC, Sills RC, Kissling GE, et al. Induction of thyroid and liver tumors by chronic exposure to 2-methylimidazole in F344/N rats and B6C3F1 mice. Arch Toxicol. 2008;82(6):399-412. (full report at [http://ntp.niehs.nih.gov/files/516final\\_web.pdf](http://ntp.niehs.nih.gov/files/516final_web.pdf))

if not likely, that the anti-cancer effect would only be seen at high, non-dietary dosages (whereas cancer causation is likely to be linear with dose). OEHHA stated that it is unaware of guidance used by any authoritative body that allows evidence of decreased tumor incidences to weigh against increased incidences.<sup>3</sup> Clearly, more *in vitro* and *in vivo* studies would have to be done to demonstrate that any anti-cancer effects are at all meaningful. But, in any case, it would make no sense to allow in foods a known carcinogen with the hope that it also would prevent cancer.

Caramel colorings manufactured with ammonia serve purely cosmetic purposes in soft drinks and other foods and beverages. The American public should not be exposed to any cancer risk whatsoever as a result of consuming such chemicals, especially when they serve a non-essential, cosmetic purpose. The risky chemicals could be quickly and easily eliminated from the food supply. We urge the FDA to revoke its approval of these caramel colorings to protect the public health.

Respectfully,

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<sup>3</sup> Alexeeff GV. OEHHA. Calif. EPA. Dec. 31, 2010. Letter sent to Murray FJ and Corash MB, Morrison and Foerster.