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MEMORANDUM

From: Martin J. Hahn
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Re: **FDA Deauthorizes Seven Synthetic Flavorings and Adjuvants as Food Additives**

On October 9, 2018 the U.S. Food and Drug Administration (FDA) issued a final rule (the Rule), revoking authorization for seven synthetic flavorings and adjuvants as food additives. Notably, FDA's rigorous scientific analysis determined that these additives do not pose a risk to public health under the conditions of their intended use. 1/ The agency acknowledges that these flavorings and adjuvants are used in very small amounts and their use results in very low levels of exposures and low risk. Nonetheless, in light of the animal data showing carcinogenicity, the agency concluded it had to withdraw their authorization as food additives as a matter of law under the Delaney clause. FDA intends to enforce the Rule's requirements only on products manufactured after October 9, 2020 containing one or more of the six synthetic flavoring substances. 2/

By way of background, the regulatory action is prompted by a food additive petition filed by Breast Cancer Prevention Partners, Center for Environmental Health, Center for Food Safety, Center for Science in the Public Interest, Consumers Union, Environmental Defense Fund, Environmental Working Group, Improving Kids' Environment, Natural Resources Defense Council, WE ACT for Environmental Justice, and Mr. James Huff, collectively "Petitioners." 3/ In January 2016, through the food additive petition process, Petitioners requested FDA amend the food additive regulations in 21 CFR § 172.515 to establish zero tolerances and no longer authorize the use of seven listed synthetic flavoring food additives recently shown to cause cancer in animals: benzophenone (also known as diphenylketone); ethyl acrylate; eugenyl methyl ether (also known as 4-allylverotrole or methyl eugenol); myrcene (also known as 7-methyl-3-methylene-1, 6-octadiene); pulegone (also known as *p*-menth-4(8)-en-3-one); pyridine; and styrene. 4/ FDA denied the petition to establish zero tolerances because the request falls outside the scope of the food additive petition process. 5/ FDA denied as moot the petition relating to styrene because, under a separate food additive petition, FDA discontinued authorization of styrene as a synthetic flavoring substances and adjuvant in food because the use has been "permanently and completely abandoned." 6/ FDA granted the petition to

1/ FDA revoked styrene's authorization based on the industry's discontinued use and has not conducted a safety assessment for styrene.
2/ 83 Fed. Reg. 50493.
3/ 83 Fed. Reg. 50490 – 50503 (Oct. 9, 2018).
4/ 83 Fed. Reg. 50491.
5/ 83 Fed. Reg. 50492.
6/ 83 Fed. Reg. 50492.

rescind authorization of the remaining six synthetic flavoring substances (i.e., all except styrene) based on data showing carcinogenicity in animals because, as a matter of law, FDA cannot consider these substances to be safe, despite FDA's findings that they are unlikely to pose a potential or significant carcinogenic risk for humans at the levels used in foods and that their use as food additives is safe for human consumption. 7/

Below, we provide more background on the Rule.

I. The Delaney Clause

The Federal Food, Drug, and Cosmetic Act (FFDCA) deems food additives unsafe and prohibited for use in human food unless approved by FDA. 8/ FDA can only approve food additives established by data as "safe" for a certain use. 9/ While FDA considers multiple factors in making a safety determination, the agency is prohibited from approving any additive found "to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for evaluation of the safety of food additives, to induce cancer in man or animal." 10/ This "extraordinarily rigid" provision, referred to as the "Delaney Clause," has been challenged and upheld by two Circuit Courts of Appeal, both of which found the Delaney Clause prohibits authorization of food additives even with only *de minimus* cancer risks. 11/ Thus, because Petitioners presented data from recent studies conducted by the Department of Health and Human Services' National Toxicology Program (NTP) that concluded the six synthetic flavoring substances induce cancer in animals, FDA was required, as a matter of law, to discontinue authorization of use of those substances as food additives. 12/

II. FDA's Toxicology Findings Found No Human Health Risk

Despite FDA's concurring with NTP conclusions that these substances pose a cancer risk for animals, FDA stressed throughout the Rule that it found no risk of cancer in humans. The table below charts the differences in FDA's conclusions regarding animal risk and human risk.

Flavoring	Animal Study Findings	FDA Human Risk Evaluations
Benzophenone 13/	Under the test conditions of the studies, benzophenone induced cancer in animals. However, benzophenone is not genotoxic and unlikely to produce cancer through a direct DNA-reactive mechanism. The findings suggest that there may be a threshold level below which benzophenone does not induce tumors in rodents.	Benzophenone is unlikely to induce tumors in humans at current use levels as a synthetic flavoring substance.

7/ 83 Fed. Reg. 50493.
8/ FFDCA §§ 301(a), (k), 409(a).
9/ FFDCA § 409(c)(3)(A).
10/ 83 Fed. Reg. 50492; FFDCA § 409(c)(5); FFDCA § 409(c)(3)(A).
11/ 83 Fed. Reg. 50492; Public Citizen v. Young, 831 F.2d 1108, 1122 (D.C. Cir. 1987); Les v. Reilly, 968 F.2d 985, 986 (9th Cir. 1992).
12/ 83 Fed. Reg. 50502.
13/ 83 Fed. Reg. 50494 – 50495.

Ethyl Acrylate 14/	Under the test conditions of the studies, ethyl acrylate is a rodent carcinogen.	Ethyl acrylate should not be considered a human carcinogen. At the current intake level, there is no concern of carcinogenicity from intake of ethyl acrylate intentionally added to food as a flavoring substance and adjuvant.
Eugenyl Methyl Ether (Methyl Eugenol) 15/	Under the test conditions of the studies, methyl eugenol induced cancer in rodents.	There is no clinical or epidemiological evidence suggesting an association between the typical dietary consumption of food items that naturally contain methyl eugenol and carcinogenic effects.
Myrcene 16/	Under the test conditions of the studies, myrcene induced renal tubular tumurs in rats and hepatocellular tumors in mice.	At its current exposure level when used as a synthetic flavoring substance in food, myrcene is unlikely to induce tumors in humans.
Pulegone 17/	Under the test conditions of the studies, pulegone is a rodent carcinogen.	At its current use level as a synthetic flavoring substance in food, pulegone is unlikely to induce urinary bladder cancer and liver neoplasms in humans and does not pose a public health concern.
Pyridine 18/	Under the test conditions, pyridine is a rodent carcinogen.	At its current exposure level when used as a synthetic flavoring substance in food, pyridine is unlikely to induce cancer in humans.

As the above table indicates, the FDA has concluded that these substances are safe.

III. The Final Rule Does Not Apply to Naturally Derived Substances

It is also worth noting that the Rule does not apply to the natural counterparts of these synthetic flavoring substances. 19/ For example, benzophenone is present in grapes, ethyl acrylate is present in pineapple, eugenyl methyl ether (methyl eugenol) is present in basil, myrcene is present in citrus fruit, pulegone is present in peppermint, and pyridine is present in coffee. 20/ FDA emphasized there is nothing in the data causing concern about the safety of foods that contain natural counterparts or non-synthetic flavoring substances extracted from food. 21/

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We will continue to monitor all developments on FDA's regulations relating to the use of food additives. Please contact us if you have any questions.

14/ 83 Fed. Reg. 50495 – 50496.
15/ 83 Fed. Reg. 50496 – 50497.
16/ 83 Fed. Reg. 50497 – 50498.
17/ 83 Fed. Reg. 50498 – 50499.
18/ 83 Fed. Reg. 50499 – 50500.
19/ 83 Fed. Reg. 50493.
20/ 83 Fed. Reg. 50493.
21/ 83 Fed. Reg. 50493.