

November 1, 2019

Mr. Julian Leichty
Office of Environmental Health Hazard Assessment
P.O. Box 4010, MS-19B
1001 "I" Street
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Re: Comments on Acetaminophen as a priority chemical for review by the Carcinogen Identification Committee

On behalf of the California Life Sciences Association (CLSA), the statewide association representing the innovative life sciences sector, a community employing more than 300,000 people at over 3,000 firms in California, we are writing to express our concerns regarding the upcoming Proposition 65 review of acetaminophen by the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment's (OEHHA) Carcinogen Identification Committee (CIC) and to assert that **listing acetaminophen as a carcinogen would be inappropriate from both an evidentiary and policy perspective.**

Focused on producing new treatments and technologies for patients who desperately need them, the life sciences sector is composed of biotechnology, medical device, pharmaceutical and diagnostics companies, research universities, and institutes throughout the Golden State – all of which depend upon a strong educational and scientific foundation in the biological sciences. In 2018, there were 3,418 life sciences companies in the state—169 more than the previous year. Of those companies, more than 1,570 are pharmaceutical and biotechnology companies, up 117 from 2017. The other 1,848 companies produce medical devices, diagnostic tests, renewable energy, research tools and other products and services, 52 more than last year. Life sciences exports increased from \$22.7 billion to \$25.2 billion, and the industry produced \$177.7 billion in revenue in 2017 (up from \$169 billion in 2016), also paying an estimated \$6.3 billion in state and local taxes in 2017.¹

Acetaminophen is one of the most commonly-used prescription and over-the-counter (OTC) drug ingredients in the U.S. – and one on which Californians have long depended for safe and effective temporary relief of pain, fever, or minor aches. Its benefits have been recognized by the U.S. Food and Drug Administration (FDA) and other health agencies globally. It is widely recommended by health care professionals especially for certain populations for whom other pain relievers, like NSAIDs, may not be appropriate. For older adults with persistent pain, infants, and patients with stomach conditions such as ulcers, or other chronic diseases, acetaminophen is often the most appropriate option for pain relief. It also is an alternative for those patients who may not need stronger medications such as opioids.

From a pharmacokinetic and scientific standpoint, acetaminophen is one of the most studied and trusted medicines available today, with more than 250 clinical studies and more than 50 years of real-world use. Extensive data generated through epidemiologic, genotoxicity, and animal carcinogenicity studies do not support a conclusion that there is a causal relationship between

¹ CLSA and PwC. *California Life Sciences Industry Report 2019*. Available at: <https://califesciences.org/wp-content/uploads/2018/11/clsa-2019-california-life-sciences-industry-report.pdf?submissionGuid=ae913577-faf6-4fac-9c39-a987f961da5c>.

acetaminophen and cancer, and no health agency globally currently deems acetaminophen to be a carcinogen. OEHHA's stated criteria for listing a chemical under Prop 65 is that it "must be *clearly shown* through scientifically valid testing" (emphasis added) to cause cancer, and the evidence for acetaminophen does not meet this standard.

More concretely, the data simply does not support the conclusion;

- 1.) According to the HID, an increase in tumors was observed in the Weisburger et al. (1973) study in NIH mice (OEHHA, 2019): p. 113). Specifically, the HID states: "*tumors were also observed in treated male Swiss mice (hepatocellular adenoma and carcinoma (combined) and urinary bladder papilloma) in the study by Weisburger et al. (1973).*"

In fact, the authors **did not** conclude that acetaminophen alone caused an increase in any tumors. Omitting the negative effect of acetaminophen alone and failing to inform that this was a tumor promotion study is neither scientifically appropriate nor valid. This study was not designed to evaluate the carcinogenicity of acetaminophen alone. It is a tumor promotion study was designed to evaluate the effect of acetaminophen when given in combination with two known carcinogens that produce tumors in a short period of time.

In many species, including mice, acetaminophen reduced the incidence of tumors caused by the two known carcinogens. This information is buried in Appendix C of the HIM on p. 343, where it states: "*Animals fed diets containing both acetaminophen and 2-AAF (or N-OHAAF) developed fewer tumors than animals exposed to 2-AAF (or N-OHAAF) alone.*"

- 2.) In the HID, OEHHA reviews (beginning on p. 154) six publications assessing the potential for APAP to produce an outcome which would increase an individual's risk for developing cancer (genotoxicity). In their description of one study (Kirkland et al., 1992), OEHHA noted that these authors, "*...used an age- and gender-matched placebo group as the comparator to the acetaminophen-treated group*" implying that this was the **only** comparison made. This is incorrect. The Kirkland et al. (1992) study design is actually superior to that of the other studies as Kirkland performed multiple comparisons. As the methods employed in the Kirkland et al., 1992 study were not fully and accurately described by OEHHA, the superior design of this study was not made clear.

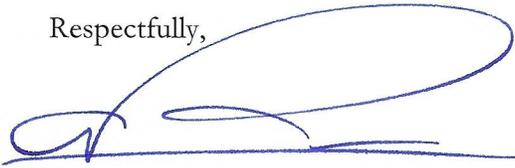
The decision before the CIC is an important public health issue of enormous consequence: getting it wrong could create significant consumer confusion, unnecessary fear, and potential harm. An unsubstantiated Prop 65 listing of acetaminophen and potential cancer warning on products containing acetaminophen could inappropriately frighten millions of consumers and drive patients to other pain medication with less favorable benefit-risk profiles for their individual medical needs, to unproven therapies, to less effective non-medical options, or perhaps even to not treating their pain at all.

Given the current pain management landscape in the US, and California specifically, it is counterproductive to be unnecessarily frightening people away from using safe, effective, and trusted pain medications like acetaminophen.

As the committee proceeds with its review of acetaminophen, we strongly encourage the CIC to recognize that acetaminophen does not meet the “clearly shown” standard required for listing as a carcinogen, and that serious consideration be given to the important role acetaminophen plays in the lives of Californians every day.

For the reasons above, **we strongly urge the CIC not to “list” acetaminophen as a carcinogen due to the lack of evidence that it has been “clearly shown” to cause cancer and due to the unnecessary confusion and fear it could cause among consumers and patients.**

Respectfully,



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