

November 4, 2019

Carcinogen Identification Committee  
Office of Environmental Health Hazard Assessment  
1001 I Street,  
Sacramento, CA 95814

Dear members of the committee:

On behalf of the Center for Environmental Health's 5,000 California supporters, we offer the following comments about the proposed Proposition 65 listing of acetaminophen.

To date, there has been numerous animal, epidemiological, meta analyses, cohort and case-control studies seeking to evaluate the potential carcinogenicity of acetaminophen; however, no large clinical trials have been conducted to assess this potential association (study participants would either be assigned to receive acetaminophen or a placebo and followed long-term, to determine cancer incidence). Therefore, many of the non-randomized studies seeking to determine this association have substantial limitations, including small sample size, short amount of follow-up time, reverse causation bias (protopathic bias), information bias, recall bias, and publication bias. Nonetheless, the existing data seems to allude to a possible relationship between the use of acetaminophen and occurrence of several cancers including renal cell carcinoma and lymphohematopoietic neoplasms (e.g., lymphoma and leukemia). It is critical to note that some of the studies did not control for confounding factors (e.g., smoking, BMI, age, sex), while others did control for some of these factors. It is important to mention that acetaminophen is the major metabolite of phenacetin, which in 1989, was added onto the Proposition 65 list as a cancer-causing agent, particularly in the kidney. In determining whether acetaminophen should be added onto Proposition 65, we suggest that the Carcinogen Identification Committee (CIC) consider the following items which we used to analyze the existing literature:

- Length of use of acetaminophen containing medications (e.g., Tylenol) prior to the onset of malignancy and age at which diagnosis was made.
- Presence of any comorbidities such as obesity, diabetes, hypertension, smoking and alcohol use history, and family history of any malignancies.

- Exposure to known cancer-causing agents related to acetaminophen, such as phenacetin.
- The methodology of the study, specifically size/power and control for confounders.

In summary, a review of the current literature indicates that there is a potential risk associated with the use of acetaminophen and increased incidence of certain types of cancers, such as renal cell carcinoma and lymphohematopoietic neoplasms; however, despite these positive associations, most of these studies had extremely small sample sizes with limitations as mentioned above. Long-term and larger-scale studies are needed to follow exposure and determine the incidence of cancer.

We know the Cancer Identification Committee will carefully consider all available data, along with the strengths and weaknesses of each study. We also know that the CIC will weigh the need to be health protective given the widespread use of this chemical. Should the CIC recommend a Proposition 65 listing, we suggest that the listing be focused on use over a long duration, or repeated use.

Sincerely,

*Michael Shahbaz*

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