



ACETAMINOPHEN:

**What It Is, How It's Used,
and the Importance of Access**

Acetaminophen Prop 65 Briefing Packet



ACETAMINOPHEN

ONE OF THE MOST COMMON DRUG INGREDIENTS IN AMERICA

PREVALENCE:

FOUND IN
MORE THAN
600
different
prescription &
over-the-counter
(OTC) medicines.¹

ACCESS:

50 MILLION

Americans use medicines containing acetaminophen each week.² This is equivalent to **5,000 PEOPLE PER MINUTE.**



SAFE & EFFECTIVE

Results from more than 250 clinical safety and efficacy studies and over six decades of use have proven acetaminophen to be a safe and effective pain reliever and fever reducer, when used as directed.³

RECOMMENDED

Acetaminophen has been identified as either a first-line or preferred OTC pain relief choice for consumers with certain chronic medical conditions by the:

AMERICAN HEART ASSOCIATION (AHA)

for patients with, or at high risk for, heart disease

NATIONAL KIDNEY FOUNDATION (NKF)

for episodic use in patients with underlying renal disease

AMERICAN GERIATRICS SOCIETY (AGS)

for persistent pain, particularly musculoskeletal pain

AMERICAN COLLEGE OF GASTROENTEROLOGY (ACG)

for patients at risk of peptic ulcer disease

THE SCIENCE

THE SCIENTIFIC EVIDENCE STRONGLY WEIGHS

AGAINST CALIFORNIA

IDENTIFYING ACETAMINOPHEN AS A KNOWN CARCINOGEN.



1 National Library of Medicine. Pillbox: Identify or Search for a Pill. Bethesda, MD: National Library of Medicine, National Institutes of Health. November 4, 2013. Accessed at: <http://pillbox.nlm.nih.gov>

2 Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. "Recent Patterns of Medication Use in the Ambulatory Adult Population of the United States: The Sloan Survey." JAMA. 287(3):337-344, 2002. <http://jama.jamanetwork.com/article.aspx?articleid=194572>

3 Response to Docket No. 1977N-0094L, FDA-Proposed Rule IAAA, McNeil Consumer Healthcare.

What is Prop 65?

Proposition (Prop) 65 (also known as The Safe Drinking Water and Toxic Enforcement Act of 1986), is a state law in California that requires the Office of Environmental Health Hazard Assessment (OEHHA) to publish a list of chemicals known to the state to cause cancer or reproductive harm. OEHHA is required to update the Prop 65 list, which currently includes over 900 substances, at least once a year.

In order to be listed under Prop 65, a chemical must be *“clearly shown through scientifically valid testing according to generally accepted principles”* to cause cancer or reproductive harm. One of the ways that a chemical can be added to the Prop 65 list is if either of two independent advisory committees of scientists and health professionals – the Carcinogen Identification Committee (CIC) or the Developmental and Reproductive Toxicant Identification Committee (DARTIC) – finds that the chemical has been clearly shown to cause cancer or reproductive harm.

Prop 65 is a “right to know law,” not a prohibition on chemicals. It establishes a requirement for manufacturers who make products with chemicals on the Prop 65 list to inform consumers that these chemicals are present in the product and they are known to the state of California to cause cancer or reproductive harm. Inclusion of a chemical on the Prop 65 list does not ban it. Rather, the law requires that companies provide a *“clear and reasonable”* warning before knowingly and intentionally exposing anyone to a listed chemical. If the exposure is low enough to pose no significant risk of cancer or is well below levels observed to cause reproductive harm, no warning is required.

Acetaminophen was chosen for review by OEHHA in part because the Prop 65 regulation emphasizes chemicals with *“widespread exposure.”* Next, the CIC will review the information on acetaminophen and cancer to determine whether acetaminophen should be listed as a carcinogen under Proposition 65. Should the CIC vote to list acetaminophen, a warning statement could be required on labels of products containing acetaminophen. In the case of acetaminophen, FDA has already stated that a cancer warning for drug products containing acetaminophen would be pre-empted under federal law given FDA’s authority over Drug Facts labeling and the Agency’s belief that a cancer warning would not be scientifically accurate and, therefore, including a cancer warning on the label would be false and misleading.



What is Acetaminophen?

Basic Information

Every day, millions of Americans rely on medicines to improve or maintain their health. One of the most commonly-used drug ingredients in the United States (U.S.) is acetaminophen, also known as paracetamol, a pain reliever and fever reducer found in more than 600 different over-the-counter (OTC) and prescription medicines.¹ More than 50 million Americans use an acetaminophen-containing medicine each week to treat pain, fever, and minor aches such as those due to the common cold, headache, backache, minor pain of arthritis, toothache, muscular aches, and premenstrual and menstrual cramps.²

Medicines Containing Acetaminophen

If an OTC medicine contains acetaminophen, it will be listed on the product package and on the label. Acetaminophen is always prominently written on the front of the box or packaging and will often be highlighted or bolded in the active ingredients section of the Drug Facts label. It is important to know that prescription medicine labels will also list “acetaminophen” or an abbreviation for it (e.g., “APAP,” “acetamin,” etc.).

COMMON MEDICINE PRODUCTS

THAT MAY CONTAIN ACETAMINOPHEN:

OVER-THE-COUNTER

Alka-Seltzer Plus®

Contac®

Coricidin® HBP

Dimetapp®

Excedrin®

Midol®

Mucinex®

NyQuil®/DayQuil®

Robitussin®

SUDAFED®

Theraflu®

Triaminic®

TYLENOL®

PRESCRIPTION

Butalbital

Endocet®

Fioricet®

Hycotab®

Hydrocet®

Hydrocodone

Lortab®

Oxycodone

Percocet®

Phenaphen®

Sedapap®

Tramadol

TYLENOL® with Codeine

Ultracet®

Vicodin®

* Acetaminophen is also contained in the generic and store brands of these medicines.

NOTE: This list is just a sample of the more than 600 different medicines that contain acetaminophen.

Benefits of Acetaminophen

Safety and Efficacy Profile

Acetaminophen is one of the most widely-used and thoroughly-studied pain-relieving and fever-reducing medicines, clinically proven over six decades of use and supported by more than 250 safety and efficacy studies.³ Acetaminophen is the OTC analgesic recommended most by healthcare professionals in the U.S. When used as directed, it is safe and effective, and it is the only OTC pain reliever and fever reducer with professional dosing available for infants under the age of 6 months in the U.S.

Special Populations that Rely on Acetaminophen

For some consumers, including older adults with persistent pain, patients with stomach conditions such as ulcers or other chronic conditions,⁴ acetaminophen is often the most appropriate option for pain relief.

In fact, acetaminophen is identified as either a first-line, preferred, or only OTC pain relief option for:



Children under the age of 6 months: Acetaminophen is commonly recommended by pediatricians to relieve pain and reduce fever in children. It is the only OTC pain reliever and fever reducer with professional dosing available for infants under the age of 6 months in the U.S.



Older consumers: Acetaminophen may be a more appropriate choice for older consumers and/or those with underlying medical issues who may be at higher risk for side effects associated with other pain relievers. The American Geriatrics Society (AGS) identifies acetaminophen as the OTC pain reliever of choice for individuals living with persistent pain. For those 60 or older, acetaminophen may be a better clinical choice because it does not carry the risk of stomach bleeding, like other pain relievers might.



Heart disease and/or stroke patients:

The American Heart Association (AHA) identifies acetaminophen as a first-line pain relief option for consumers with, or at high risk for, heart disease.



People with high blood pressure:

Acetaminophen may be a more appropriate choice of pain reliever for those with high blood pressure as it does not elevate blood pressure like nonsteroidal anti-inflammatory drugs (NSAIDs) can.



Patients with a history of stomach bleeding, stomach ulcers, or heartburn:

Acetaminophen may be a more appropriate choice of pain reliever because it does not irritate the stomach.



People with asthma:

Acetaminophen may be a more appropriate choice of pain reliever for many people with asthma because it does not make asthma symptoms worse as other pain relievers may.



Patients with kidney disease:

The National Kidney Foundation (NKF) identifies acetaminophen as the OTC pain reliever of choice for occasional use in people living with kidney disease.

⁴ Curfman G. FDA strengthens warning that NSAIDs increase heart attack and stroke risk. Harvard Health Blog. 22 Aug. 2017. Retrieved from: <https://www.health.harvard.edu/blog/fda-strengthens-warning-that-nsaids-increase-heart-attack-and-stroke-risk-201507138138>.



The Science Behind Acetaminophen

In order to be listed under Prop 65 in California, acetaminophen must be “clearly shown through scientifically valid testing according to generally accepted principles” to cause cancer. **The scientific evidence strongly weighs against California identifying acetaminophen as a known carcinogen.**

An up-to-date review of the scientific evidence based on input from leading experts in the fields of epidemiology, genotoxicity, and animal carcinogenicity found that the weight of the scientific evidence clearly demonstrates **there is no causal association between acetaminophen use and cancer.**⁵

“ FDA has determined that the currently available evidence does not support a conclusion that acetaminophen in FDA-regulated products causes cancer. Accordingly, a Proposition 65 cancer warning on the labeling of products containing acetaminophen would not be scientifically accurate, and such labeling would be false or misleading. Specifically, this warning could mislead consumers into believing that using a drug product containing acetaminophen would increase their risk for developing cancer. ”

– The U.S. Food and Drug Administration⁸

There is no convincing human data to support carcinogenicity of acetaminophen.

Numerous epidemiologic studies have evaluated whether the use of acetaminophen is associated with various types of cancer. For the large majority of cancer types, there is no increased risk with acetaminophen use, even when it is taken for longer periods of time. Although some studies have observed a small increase in risk, these results are considered inconclusive based either on limited data, the inherent limitations of studying humans when one can't account for all the relevant variables, or conflicting results from other studies showing no increase in risk.⁶

Animal test results are reassuring and support the safety of acetaminophen.

Preclinical studies have shown no meaningful link between acetaminophen exposure and cancer. The International Agency for Research on Cancer (IARC) examined the preclinical study results and their overall evaluation was that acetaminophen is not classifiable as to its carcinogenicity to humans.^{*7}

The U.S. Food and Drug Administration (FDA) determined that the currently available evidence – nonclinical and clinical – does not support a conclusion that exposure to acetaminophen in FDA-regulated products causes cancer.

FDA has reviewed acetaminophen labeling on numerous occasions and has not labeled acetaminophen a carcinogen or a mutagen.⁸

5 CHPA submission to the California Office of Environmental Health Hazard Assessment. November 2019. Accessed at: <https://oehha.ca.gov/proposition-65/comments/comment-submissions-announcement-carcinogen-identification-committee-meeting>

6 Weiss NS. Use of acetaminophen in relation to the occurrence of cancer: a review of epidemiologic studies. *Cancer Causes Control*. 2016;27(12):1411-1418.

*Acetaminophen was classified as Group 3 by IARC (Group 1 – Carcinogenic to humans, Group 2A – Probably carcinogenic to humans, Group 2B – Possibly carcinogenic to humans and Group 3 -Not Classifiable as to its carcinogenicity in humans).

7 International Agency for Research on Cancer (IARC) - Summaries & Evaluations Volume: 73 (1999) (p. 401)

8 FDA submission to the California Office of Environmental Health Hazard Assessment. November 2019. Accessed at: <https://oehha.ca.gov/proposition-65/comments/comment-submissions-announcement-carcinogen-identification-committee-meeting>

Likely Unintended Consequences of Prop 65 Listing

A significant amount of information is available demonstrating that acetaminophen does not increase the risk of cancer. **Listing acetaminophen under Prop 65 would not only contradict the weight of the scientific evidence, but it would also likely confuse consumers when they decide on pain relief options.** This could lead some sensitive consumers to switch to pain relievers that present greater overall safety concerns for their personal health circumstances. Consumer studies and other research have shown that when access to their preferred dose of acetaminophen is compromised, as many as 40 percent of consumers will switch to an OTC NSAID (aspirin, ibuprofen, or naproxen) without understanding the potential for NSAID-related health risks, including heart attack and stroke.^{9,10}



While this research explored compromised access in terms of physical barriers to access (i.e. behind the counter, out of stock), it is reasonable to assume that inclusion of a Prop 65 warning on products would serve as a psychological barrier to access for some, thereby pushing consumers to pain medications with a potentially less favorable benefit-risk profile for their individual medical need, to an unproven drug, to non-medical options, or to non-treatment of their pain at all.

Also, given the current landscape of pain management in the U.S., it is counter-productive to unnecessarily deter people from using safe, effective, and trusted pain medications like acetaminophen.

The U.S. Department of Health and Human Services (HHS) identifies acetaminophen as an important alternative to opioids for healthcare professionals to consider. Its draft report entitled “Draft Report on Pain Management Best Practices: Updates, Gaps, Inconsistencies, and Recommendations” recommends acetaminophen as a first-line class of medication following standard dosing schedules for non-neuropathic, non-cancer pain, to be utilized with other non-pharmacologic treatments as an alternative to opioids.

“ A decision to list acetaminophen under Proposition 65 will cause consumer confusion and could negatively impact patient compliance with non-opioid pain management regimens and even result in an increase in preference to opioid medication. ”

– California Dental Association¹¹

9 Alliance For Aging Research, Pain Study Report_Nationwide Survey of U.S. Adults, December 2014. Retrieved from: <http://agingresearch.org/CustomPages/view/64>

10 Curfman, G. July 13, 2015. FDA strengthens warning that NSAIDs increase heart attack and stroke risk. Harvard Health Publishing. Retrieved from: <https://www.health.harvard.edu/blog/fda-strengthens-warning-that-nsaids-increase-heart-attack-and-stroke-risk-201507138138>

11 California Dental Association submission to the California Office of Environmental Health Hazard Assessment. November 2019. Accessed at: <https://oehha.ca.gov/proposition-65/comments/comment-submissions-announcement-carcinogen-identification-committee-meeting>



What Other Experts are Saying

Since OEHHA released the HIM, experts, including FDA and over 20 state and national groups representing patients, clinicians, and health advocates, have expressed deep concern about the possibility of acetaminophen being added to the Prop 65 list of chemicals because such a decision would go against the extensive evidence base.¹²

California Dental Association: “There simply is not compelling evidence to conclude there is an increased risk of cancer due to use of acetaminophen. This should be sufficient to exclude acetaminophen from being added to Proposition 65 list of carcinogens.”

California Life Sciences Association: “We are writing to express our concerns regarding the upcoming Proposition 65 review of acetaminophen...and to assert that listing acetaminophen as a carcinogen would be inappropriate from both an evidentiary and policy perspective.”

California Rheumatology Alliance: “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), by other health agencies globally, and it is widely recommended by rheumatologists especially for certain populations for whom other pain relievers, like NSAIDs, may not be appropriate. For patients with 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.”

Protecting Access to Pain Relief*: “The PAPR Coalition is concerned that listing acetaminophen as a carcinogen under Proposition 65 without extensive scientific evidence supporting the claim may dissuade consumers from choosing the OTC pain relief options deemed most appropriate for their condition by their physician. This is especially true given recent research indicating no evidence of increased risk of carcinogenicity linked to acetaminophen use for a large majority of cancer types.”

U.S. Food and Drug Administration: “...we do not find that currently available nonclinical and clinical data support a conclusion that such exposure causes cancer. We are concerned, too, about the unintended risks of adding an unjustified warning to labeling. A carcinogenicity warning for acetaminophen may drive patients who are doing well on acetaminophen to other pain relievers, each of which has its own risk profile. An increase in opioid use would be especially concerning. We therefore do not think a warning would be in the best interests of public health.”

12 Comment Submissions to the California Office of Environmental Health Hazard Assessment. November 2019. Accessed at: <https://oehha.ca.gov/proposition-65/comments/comment-submissions-announcement-carcinogen-identification-committee-meeting>

* The PAPR Coalition represents: Alliance for Aging Research, American Association of Kidney Patients, American Chronic Pain Association, American Gastroenterological Association, The Gerontological Society of America, National Minority Quality Forum, Renal Physicians Association, TransplantFirst Academy, and Veterans Transplantation Association.





The Consumer Healthcare Products Association (CHPA) is the 138-year-old national trade association representing the leading manufacturers and marketers of over-the-counter (OTC) medicines and dietary supplements. Every dollar spent by consumers on OTC medicines saves the U.S. healthcare system more than \$7, contributing a total of \$146 billion in savings each year. CHPA is committed to empowering self-care by preserving and expanding choice and availability of consumer healthcare products. For more information, visit chpa.org.

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