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Members of the Carcinogen Identification Committee

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Proposition 65 Implementation
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Re: Prioritization of Acetaminophen

Dear Chairperson Mack and Members of the Carcinogen Identification Committee

The Consumer Healthcare Products Association (CHPA) requests the Proposition 65 Carcinogen Identification Committee (CIC) recommend a “low priority” for the review of acetaminophen. CHPA, founded in 1881, is a member-based association representing the leading manufacturers and distributors of nonprescription, over-the-counter (OTC) medicines and dietary supplements.

Summary

Acetaminophen should be assigned a “low priority” for several reasons:

- There is no convincing epidemiologic evidence of a link between acetaminophen exposure and cancer in humans.
- There is limited evidence of carcinogenicity of acetaminophen in animals.
- No new convincing evidence has been presented since OEHHA prioritized acetaminophen as “low” priority in 1997.
- Since the 1997 prioritization, FDA has reviewed and approved a New Drug Application for OFIRMEN™, a prescription only intravenous formulation of acetaminophen. This approval included a review of carcinogenicity data that indicated no (based on mice and male rats) or equivocal (based on female rats) evidence of carcinogenic activity.
- The public health benefits of acetaminophen in treating pain and fever safely and effectively are well recognized.
Introduction and Background

On October 13, the CIC will consider the prioritization of 39 chemicals identified by OEHHA in the Notice entitled, “Prioritization: Chemicals for Consultation by the Carcinogen Identification Committee” dated July 22, 2011 (OEHHA Notice). To identify these 39 chemicals, OEHHA conducted a preliminary toxicological evaluation for the chemicals discussed at 2007 and 2008 meetings of the CIC. The OEHHA Notice provided an exposure assessment, along with human data, animal data and other relevant data evaluating carcinogenicity potential. OEHHA compiled a summary of the relevant studies that were identified during the preliminary toxicological evaluation.

The following sections of this submission briefly summarize the available data relevant to an assessment of the potential carcinogenicity of acetaminophen, following the general categories in the summary table in the OEHHA Notice. In addition, a summary of a recent review of the potential carcinogenicity of acetaminophen conducted by the FDA prior to the approval of a prescription acetaminophen product is also provided. When all of the evidence is considered, it is apparent that acetaminophen should not be a priority for further review by the CIC. CHPA believes the available evidence supports a “low priority” recommendation for acetaminophen.

Human Data

In 1990 and again in 1999, the International Agency for Research on Cancer (IARC) concluded that there was inadequate evidence for the carcinogenicity of acetaminophen in humans, and that overall, acetaminophen could not be classified as to its carcinogenicity to humans (Group 3). In May 1997, OEHHA, as part of its Proposition 65 prioritization process, determined that there was a “low level of carcinogenicity concern over acetaminophen” (OEHHA, 1997). More recently, in November 2010, FDA approved a New Drug Application (NDA) for OFIRMEV™, a prescription acetaminophen intravenous formulation, with no carcinogenicity concerns identified.

The Summary Table in the OEHHA Notice prioritization document correctly indicates there are analytic epidemiology studies that included acetaminophen. Appendix A in the OEHHA assessment identifies a number of case-control studies and cohort studies published since May 1997 that included acetaminophen, often as one of many exposures evaluated in relation to cancer. Results for epidemiologic studies included in Appendix A were inconsistent for all types of cancers evaluated and continue to support no clear association between acetaminophen use and development of cancer. While some studies reported an increased risk with acetaminophen use, most studies reported no increased risk.

It should be noted that because of the observational nature of cohort and case-control epidemiologic studies, methodologic concerns exist, including recall bias and confounding by indication. The latter is of particular concern for acetaminophen, since acetaminophen is often recommended to those who are ill for the relief of pain of their developing and undiagnosed condition (e.g., cancer) and may be more likely to be falsely associated with that condition.

Most epidemiologic studies in the July 2011 OEHHA Appendix A reported that acetaminophen use was not associated with an increased risk of cancer and have included studies of the following cancer types: ovarian, breast, endometrial, colon/rectal, renal, bladder, urothelial, prostate, non-Hodgkin’s lymphoma, leukemia, esophageal, and glioblastoma multiforme. In a few studies, a protective effect of acetaminophen use, i.e., a reduced risk of cancer, was reported. Most recently, a study examining the relationship between analgesic use and renal cell cancer risk in the Nurses’ Health Study and the Health Professionals Follow-Up Study reported no association between acetaminophen use and renal cell cancer risk over 16-20 years (Cho, 2011).
In summary, a review of the studies in Appendix A and one more recently published study does not support a change in the current “low” priority level for acetaminophen.

Animal Data

OEHHA last reviewed the epidemiologic, animal carcinogenicity and mutagenicity data for acetaminophen in 1997. The OEHHA determination was based in part on the extensive IARC (1990) review of the available literature. The 1990 IARC concluded that there was limited evidence for carcinogenicity of paracetamol [acetaminophen] in experimental animals and inadequate evidence of carcinogenicity of paracetamol in humans. Since the 1997 review of acetaminophen by OEHHA, two additional scientific reviews have occurred. Bergman et al (1996) conducted an extensive review of the carcinogenicity and mutagenicity of acetaminophen, reaching similar conclusions to the IARC and OEHHA determinations. In 1999 IARC again reviewed acetaminophen, including the results of the National Toxicology Program Bioassays in rats and mice (NTP, 1993), as well as other laboratory-based and epidemiologic studies. This IARC assessment concluded that there was inadequate evidence in humans and in experimental animals for the carcinogenicity of paracetamol.

Genotoxicity

Since acetaminophen was first marketed in the United States in 1953, it has been extensively evaluated for potential genotoxicity using both in vitro and in vivo assays with a variety of endpoints. This research used many different testing models and included human and rodent primary cell cultures and cell lines. Regulatory and peer reviewed published data support lack of mutagenicity; however, the assays measuring chromosomal damage present mixed results. These inconsistent results indicate that acetaminophen is not directly DNA damaging; rather, it is a secondary effect to toxicity (Djordjevic et al. 1986, Brunborg et al. 1995, Oshida et al. 2008). More recently (Nov 2010), FDA’s review of a new submission, OFIRMEV™ (acetaminophen) for IV injection resulted in no concerns regarding genotoxicity which further supports assignment of acetaminophen of as “low priority.”

Recent Authoritative Body Review of Acetaminophen

Within the last year, the Food and Drug Administration (FDA) reviewed and approved (November 2010) a New Drug Application for OFIRMEV™, a prescription only, intravenous formulation of acetaminophen. This included an extensive review of available data including animal carcinogenicity studies that indicated no (based on mice, male rats) or equivocal (based on female rats) evidence of carcinogenic activity. This finding was endorsed by the FDA’s Executive Carcinogenicity Assessment Committee. Conclusions regarding mutagenicity data supported previously reported findings and were mixed (Ames negative, threshold effect in clastogenicity testing and positive results in in vitro mouse lymphoma and in vitro chromosomal aberration assay using human lymphocytes). This recent and comprehensive review of scientific data by FDA supports a low priority for acetaminophen.

Exposure and Public Health Importance

OEHHA has correctly identified “widespread exposure” to describe acetaminophen. This is not surprising, given the well-recognized public health benefits of acetaminophen in treating fever and pain. Acetaminophen is the most
commonly used drug ingredient in the U.S. In any given week, nearly 25% of adults report using an acetaminophen-containing product, including over-the-counter single-ingredient and combination products as well as prescription (Rx) narcotic/acetaminophen combination medicines (Kaufman 2002). FDA (2009) has acknowledged the importance of acetaminophen in effectively relieving pain and fever. Over-the-counter (OTC) acetaminophen effectively treats a wide variety of pain, including dental, muscle, headache, menstrual cramps and osteoarthritis. Its importance as first-line therapy in treating osteoarthritis pain cannot be overstated. Many professional organizations, including the American College of Rheumatology (2000), the Osteoarthritis Research Society International (Zhang 2008), and the Agency for Healthcare Research and Quality (2009) recommend acetaminophen as first-line therapy for treating osteoarthritis.

Conclusion

When all of the evidence is considered, it is apparent that acetaminophen should not be a priority for further review by the CIC. There is no convincing human data to support carcinogenicity. FDA’s recent review of a prescription acetaminophen product did not identify any concerns regarding the carcinogenicity of acetaminophen. There is limited evidence of carcinogenicity of acetaminophen in animals. Human exposure to acetaminophen is widespread, and there is good reason for it. It provides a significant public health benefit. The well-recognized public health benefits should not be disregarded. CHPA believes the available evidence supports a “low priority” recommendation for acetaminophen.

We appreciate the opportunity to submit these comments. We look forward to participating in the October 12-13, 2011, CIC meeting.

Sincerely,

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Vice President, Regulatory & Scientific Affairs
References


