

## Acetaminophen

*N*-(4-Hydroxyphenyl) acetamide

Acetaminophen (paracetamol) is an aromatic amide. It is part of the class of drugs known as "aniline analgesics," and it is widely used as an over-the-counter analgesic and antipyretic. Acetaminophen was approved by the Food and Drug Administration for sale as a nonprescription drug in 1960. Acetaminophen is available in pure form as various trade-name preparations for oral use. It is also combined in over 20 preparations with other drugs.

Acetaminophen passed the human and animal data screens, underwent a preliminary toxicological evaluation, and is being brought to the Carcinogen Identification Committee for consultation. This is a compilation of the relevant studies identified during the preliminary toxicological evaluation.

### Epidemiological data

The epidemiologic evidence was last reviewed comprehensively by the International Agency for Research on Cancer (IARC) in 1999. Since the IARC review, approximately 60 new epidemiology studies have reported findings for acetaminophen and cancer risk, and a number have reported statistically significant positive associations.

See Appendix A for abstracts of epidemiology studies on acetaminophen published since or not included in the IARC (1999) review, with results highlighted (e.g., underlined).

### Animal carcinogenicity data

- Long-term dietary studies in rats
  - 27-month study in male Sprague-Dawley rats: Johansson (1981)
    - *No treatment-related tumor findings*
  - Two-year studies in male and female F344/N rats: NTP (1993)
    - *Increase in mononuclear cell leukemia (by pairwise comparison and trend) in females*
    - *No treatment-related tumor findings in males*
  - Two-year dietary exposure and additional 26-week observation in male and female F344/ DuCrj rats: Hiraga and Fujii (1985)
    - *No treatment-related tumor findings in males or females*
  - 18-month studies in male and female Leeds rats: Flaks *et al.* (1985)
    - *Increases in neoplastic nodules (adenomas) of the liver, bladder papilloma, and combined bladder papilloma and carcinoma (by pairwise comparison and trend) in males*
    - *Increases in neoplastic nodules (adenomas) of the liver (by pairwise comparison and trend) and combined bladder*

*papilloma and carcinoma (by pairwise comparison) in females*

- Long-term dietary studies in mice
  - 31-month studies in male and female B6C3F<sub>1</sub> mice: Amo and Matsuyama (1985), as reviewed in IARC (1990, p. 311)
    - *No treatment-related tumor findings in males or females*
  - Two-year studies in male and female B6C3F<sub>1</sub> mice: NTP (1993)
    - *No treatment-related tumor findings in males or females*
  - 18-month studies in male and female IF mice: Flaks and Flaks (1983)
    - *Increase in liver adenoma, liver carcinoma, and combined liver adenoma and carcinoma (by pairwise comparison and trend) in males*
    - *Increase in liver adenoma and combined liver adenoma and carcinoma (by pairwise comparison and trend) in females*
  - 70-week study in male B6C3F<sub>1</sub> mice: Hagiwara and Ward (1986)
    - *No treatment-related tumor findings*
  - 11-month study in female NIH mice: Weisburger *et al.* (1973), as reviewed in Flaks *et al.* (1985)
    - *Increase in bladder epithelial tumor*
- Tumor promotion studies in rats
  - Male Fischer 344 rats received N-nitrosoethyl-N-hydroxyethylamine as an initiator in drinking water for two weeks, followed one week later with acetaminophen in the diet for 29 weeks: Tsuda *et al.* (1984), as reviewed in IARC (1990, pp. 312-313)
    - *Increase in renal cell adenoma*
  - Male Fisher 344 rats received N-nitrosobutyl-N-(4-hydroxybutyl)amine as an initiator in drinking water for four weeks, followed by acetaminophen in the diet for 32 weeks: Kurata *et al.* (1986), as reviewed in IARC (1990, p. 313)
    - *No acetaminophen treatment-related tumor findings*
- Tumor promotion study in mice
  - Male B6C3F<sub>1</sub> mice received a single intraperitoneal injection of N-nitrosodiethylamine as an initiator, followed two weeks later with acetaminophen in the diet for up to 70 weeks: Hagiwara and Ward (1986), as reviewed in IARC (1990, p. 312)
    - *No acetaminophen treatment-related tumor findings*

## Other relevant data

- Genotoxicity
  - *In vitro* genotoxicity: Bergman *et al.* (1996); IARC (1990, pp. 318-319, 321); IARC (1999, pp. 431-436); Matsushima *et al.* (1999); NTP (1993)
    - Mutations in *Salmonella typhimurium* (*positive and negative*)
    - Mutations in *Escherichia coli* (*negative*)
    - Sex-linked recessive lethal mutations in *Drosophila* (*negative*)
    - Somatic mutations and recombination in the *Drosophila* SMART-test (*positive*)
    - Mutations in C3H/10T $\frac{1}{2}$  mouse embryo fibroblasts, V79 hamster cells, and Chinese hamster ovary (CHO) cells (*negative*)
    - Mutations in mouse lymphoma L5178Y cells (*positive*)
    - Chromosome aberrations (CA) in CHO cells (*positive*), Chinese hamster V79 cells (*positive*), and human lymphocytes (*positive*)
    - Sister chromatid exchanges (SCE) in CHO cells (*positive*), Chinese hamster V79 cells (*positive*), human peripheral lymphocytes (*positive and negative*), and human fibroblasts (*negative*)
    - Micronuclei (MN) in the Chinese hamster lung cell line CHL/IU (*positive*), and rat kidney fibroblasts (*positive*)
    - DNA single strand breaks in CHO cells (*positive*), hamster lung V79 cells (*positive*), and rat hepatoma cells (*negative*)
    - Unscheduled DNA synthesis (UDS) in mouse hepatocytes (*positive*), rat hepatocytes (*positive and negative*), Syrian hamster hepatocytes (*negative*), hamster V79 cells (*negative*), and guinea pig hepatocytes (*negative*)
    - Binding to protein and DNA in a cell-free system (*positive*)
    - Binding to DNA and RNA in cultured human granulocytes and HL-60 cells (*positive*)
    - Cell transformation in C3H/10T $\frac{1}{2}$  mouse embryo cells (*positive*)
  - *In vivo* genotoxicity: Bergman *et al.* (1996); Hanston *et al.* (1996); IARC (1990, pp. 318-319, 321); IARC (1999, pp. 431-436); Oshida *et al.* (2008)
    - CA in human peripheral blood lymphocytes (*positive and negative*), human buccal mucosa cells (*positive*), mouse spermatocytes (*negative*) mouse bone marrow cells (*positive and negative*), rat bone marrow cells (*positive*), and Chinese hamster bone marrow cells (*negative*)

- SCE in human peripheral lymphocytes (*positive*) and mouse bone marrow cells (*positive*)
  - Aneuploidy in rat embryos exposed transplacentally (*positive*)
  - MN in mouse bone marrow cells (*positive and negative*), and rat bone marrow cells (*positive*)
  - DNA single strand breaks in mouse liver (*positive*) and kidney (*negative*), and rat liver and kidney (*negative*)
  - UDS in male rat liver (*negative*)
  - DNA damage (comet assay) in mouse liver (*positive*)
  - Oxidative DNA damage, as measured by 8-hydroxydeoxyguanosine, in rat bone marrow (*positive*)
  - Binding to liver and kidney DNA and protein in mice (*positive*)
  - Formation of DNA adducts in F344 rats, assessed by <sup>32</sup>P-postlabelling (*negative*)
- Inhibition of nucleotide excision repair: Brunborg *et al.* (1995)
- Metabolism
  - Acetaminophen is a major metabolite of phenacetin, a Proposition 65 carcinogen, and of acetanilide, a weak liver carcinogen in rodents
  - Acetaminophen metabolite N-acetyl-para-benzoquinoneimine (NAPQI): Dybing *et al.* (1984)
    - DNA single strand breaks in hepatoma cells (*positive*)
  - Acetaminophen metabolite N-hydroxyacetaminophen
    - DNA synthesis inhibition in rat kidney cells (*positive*): Djordjevic *et al.* (1986)
    - MN induction in rat kidney cells (*positive*): Dunn *et al.* (1987)
  - Acetaminophen metabolite 4-aminophenol: NTP (1993)
    - Mutations in mouse lymphoma cells (*positive*)
    - SCE in human lymphocytes (*positive*)
    - *In vivo* CA and MN in mouse bone marrow cells (*positive*)

## Reviews

- IARC (1990, 1999); Rannug *et al.* (1995)

## References<sup>1</sup>

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<sup>1</sup> Excerpts or the complete publication have been provided to members of the Carcinogen Identification Committee, in the order in which they are discussed in this document.

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