

Overview of Acetaminophen Label Warnings

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Advisory Panel Conclusions (1977)

- Safe and effective for OTC use.
- Relatively free of adverse effects in most age groups, even in the presence of a variety of disease states.
- Adult Dose
 - 325 to 650 mg every 4 hours not to exceed 4,000 mg in 24 hours for \leq 10 days.
- Children's Dose
 - Age-based dosing for children \geq 2 years based on a standard 81-mg dosage unit.



Advisory Panel Conclusions (1977)

- Liver disease may prolong half-life of unchanged drug.
- Could not conclude that the observed increased half-life will increase the potential or severity of hepatotoxicity.
- Definitive studies are not available on whether or not acetaminophen should be used in patients with certain preexisting liver diseases.
- High priority should be given to well-designed studies to resolve this issue.



Advisory Panel Conclusions (1977)

- Harmful effects on the liver are well-documented in acute overdose.
- Single doses < 15 gm are not usually associated with serious liver damage.
- Overdose may result in severe liver damage and a warning regarding this effect is obligatory.



Advisory Panel Conclusions (1977)

Recommended warning:

**“Do not exceed recommended dosage
because severe liver damage may occur”.**



Comments Opposed to Warnings

- Places the responsibility of recognizing organ damage on the consumer.
- May be misunderstood or may alarm or cause anxiety in consumers who use drugs rationally.
- May encourage suicidal persons to abuse acetaminophen.
- Inappropriate for children's products because there is a lack of documented fatalities in children from acute overdose.



Comments For A Liver Warning

- There are no unique signs of toxicity, such as ringing in the ears (tinnitus), and symptoms of toxicity do not appear until a few days after the overdose.
- Consumers are increasing use of acetaminophen.
- Fatalities and liver damage have occurred in children.
- Warning may discourage consumers from exceeding the recommended daily dosage.



Tentative Final Monograph (TFM) (1988)

Adult Dose

- 325 to 650 mg every 4 hours;***
- 325 to 500 mg every 3 hours;***
- 650 to 1,000 mg every 6 hours not to exceed 4,000 mg in 24 hours for \leq 10 days.***

Children's Dose

Age-based dosing for children \geq 2 years based on an 80- or 81-mg or a 325-mg dosage unit



FDA Conclusions (1988)

- **Data inadequate to support the warning within the recommended labeled dose.**
- **Warnings need not specify toxic effects of particular organs of the body caused by acute overdose.**
- **Liver damage can occur from overdosage and a warning statement is warranted.**
- **Lack of symptoms could delay the use of antidote.**
- **Prompt medical attention is essential to the proper management of acetaminophen overdose.**



FDA Conclusions (1988)

Recommended Warning

Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately. *Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms.*



Comments for an alcohol warning

- 75 reports cited of liver damage in alcohol abusers who used acetaminophen for labeled claims.
- Animal data confirms increased liver toxicity.
- Chronic alcohol ingestion induces microsomal enzymes, increasing formation of the toxic metabolite (NAPQI) and interferes with it's detoxification by depleting hepatic glutathione (GSH).
- Recommended a reduced (2 gm) maximum daily dose for alcohol abusers.



Comments Opposed To Warning

- Existing data provide no rational basis for a warning.
- Majority of reports involved subjects with a history of alcohol abuse and use far in excess of the maximum daily dose.
- Other studies were cited that disagreed that animal and human data have demonstrated increased liver toxicity.



NDAC Meeting (June 1993)

Data Reviewed:

- Issues raised in TFM comments.
- Published reports of acetaminophen-induced liver toxicity in alcohol users at various doses.
- Acetaminophen metabolism in alcohol abusers.
- Microsomal enzyme induction in subjects with liver disease.
- Effect of alcohol abuse on acetaminophen overdose.
- Animal data (effects of ethanol and diet on metabolism and on glutathione levels).



Questions to NDAC (June 1993)

- Does the data support a warning for alcohol abusers?
- What population is at risk (drinks rarely, social, or abusers) and at what dose?
- Benefit/risk considerations: will alcohol abusers switch to other ingredients that have equivalent or greater risks?
- What information should be included (organ-specific, alcohol amount, etc.)?
- Are data sufficient to support a reduced maximum daily dose (2 gm) for alcohol abusers, if so, what it should be?



NDAC Conclusion (June 1993)

- **Alcohol abusers are at increased risk.**
- **Warning should specifically refer to possible liver damage.**
- **Warning could cause alcohol abusers to switch to other products with equivalent or greater risks.**
- **Should not be implemented until NDAC considers the risk for other analgesic ingredients.**
- **Insufficient data to recommend a reduced maximum daily dose for alcohol abusers.**



FDA Conclusions (1997)

- **Chronic heavy alcohol use or abuse has a significant effect on the metabolism and detoxification of NAPQI.**
- **Alcohol abusers are at increased risk and a warning is warranted for adult products.**
- **Organ specific warnings are more effective than general warnings.**
- **Insufficient data to recommend a reduced maximum daily dose for alcohol abusers.**
- **Labeling should recommend contact with a physician.**



Alcohol Warning Final Rule (1998)

Alcohol warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take acetaminophen or other pain relievers/fever reducers. Acetaminophen may cause liver damage.

