**Another Chapter in the Long History of Exposing the Dangers of the Most Popular Drug in America**

**Worst Pills Best Pills Newsletter article July, 2009**

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Acetaminophen, the unpronounceable name for the most widely used pain reliever in the United States (TYLENOL), can destroy the liver in ordinary or near-ordinary doses. That fact will be news to many consumers but is old hat to liver specialists, and now was finally acknowledged officially late in April 2009 by the Food and Drug Administration (FDA).

That it took the FDA 31 years to reach this conclusion speaks volumes about both the overly casual way that many Americans swallow pain relievers, and also about the holes in the regulatory system for drug safety — especially when it involves drugs found in nearly every American medicine cabinet, as acetaminophen is through popular brands like TYLENOL and more than 100 other products.

In 1977, an FDA advisory panel rocked the highly competitive world of over-the-counter (OTC) pain relievers when it proposed that acetaminophen, which had only become OTC a few years before, carry this warning on all packages: "Do not exceed the recommended dosage because severe liver damage may occur."

The makers of aspirin products, which carry their own risk of stomach bleeding but no risks to the liver, quickly trumpeted their own safety but in short order had to mute their horns when in the 1980s Reye's Syndrome, a deadly disorder in children with viral diseases, was linked to aspirin consumption, and a whole generation of parents stopped giving their children baby aspirin and switched to what was then the only OTC alternative, acetaminophen.

The Johnson & Johnson subsidiary, McNeil, which makes TYLENOL, fought hard to persuade the FDA that "severe liver damage" was an unnecessarily alarming statement for the official product label because, it maintained, the only people who suffered such injury had taken massive overdoses, usually in suicide attempts. In 1988, the FDA issued a "tentative final monograph" agreeing with McNeil's position, despite the accumulation of a series of case reports in the liver disease literature that "therapeutic misadventures" at or near recommended dosing levels caused acute liver failure. Most of the reports concerned alcohol drinkers who took three or more drinks a day and thus primed their livers to convert acetaminophen to a toxic byproduct through the same enzyme (cytochrome P450 2E1) that the liver uses to process large amounts of alcohol. In 1999, the FDA mandated an alcohol warning on acetaminophen labels.

As the regulatory gears ground slowly, liver transplant centers and intensive care units across the country treated a steady stream of acetaminophen victims: desperately ill patients every week who had succumbed to sudden liver failure. Their histories often involved generous dosing at or a little more than the recommended four grams a day (eight "extra-strength" tablets of 500 milligram acetaminophen). Often the patients did not realize they were exceeding the dosing limit because they were taking more than one pain reliever with acetaminophen. (For example, prescription pain relievers like acetaminophen and oxycodone [PERCOCET] and propoxyphene and acetaminophen [DARVOCET] contain acetaminophen, in addition to a narcotic, as indicated by the "-cet" in the name.) In less than half of these cases the patients were alcoholics.

A multi-center report led by investigators at UT-Southwestern documented that acetaminophen ingestion is the leading cause of acute liver failure in the United States. Acetaminophen ingestion accounted for 46 percent of cases, outstripping viral hepatitis and dwarfing liver failure due to all other drugs combined. The FDA estimates that around 400 Americans die annually due to acetaminophen toxicity.

The new package warning, which takes effect one year from now (a blink of an eye in the multi-decade history of this issue before the FDA), is very close to the original proposal from 1977. The packaging will state on 500-mg products:

***Liver warning: This product contains acetaminophen.Severe liver damage may occur if you take more than eight tablets in 24 hours, the maximum daily amount.***

It will also warn against using it with other acetaminophen products or with alcohol use of three or more drinks a day. The FDA rejected a request from the TYLENOL manufacturer McNeil to water down the warning by removing the word "severe" and adding the word "overdose," which the agency said could lead consumers to believe they had to greatly exceed the recommended dosage before jeopardizing their livers.

Two questions remain: Why did the FDA wait until 2009 to require what liver disease experts asked it to do in 1977? And what more needs to be done to protect the public?

The "final rule" published in April in the Federal Register makes it clear that many questions about who is at risk for acetaminophen poisoning remain unanswered. The FDA is calling for large safety studies, but it lacks any power to force manufacturers to fund them and has no budget for its own safety investigations. The studies that have been published over the years typically have featured a few score of patients whose cases are cobbled together on shoestring research budgets. An additional impediment to clear answers is that unlike most other advanced countries, the United States has only a voluntary system for adverse event reports for drugs and medical devices.

Other countries also restrict acetaminophen sales to discourage inadvertent overuse. The British Parliament passed legislation in 1998 limiting package size and mandating blister packaging which limits impulsive use and the likelihood of overdosing. These measures have been associated with a significant reduction in the number of intensive care admissions and liver transplantation for acetaminophen. The FDA may take up that issue at another hearing in June 2009. Items for consideration should include unbundling of the narcotic/acetaminophen compounds, since these have recently been associated with many unintentional overdoses and should certainly include discussion of limiting package size, since 500-tablet bottles and advertising that emphasizes its safety don't fit with the overall picture of a potentially lethal drug.