C24 Acetaminophen Carcinogenic Dose Response Assessment

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The goal of this presentation are to (1) to estimate the carcinogenic potency of acetaminophen, (2) to illustrate a lack of consistency in the evaluation and regulation of threshold carcinogens; and (3) to examine U.S. Environmental Protection Agency's (US EPA) methodology for determining cancer potency estimates for environmental carcinogens.

This presentation will impact the forensic science community by showing an inconsistency in the evaluation and regulation of carcinogenic compounds allows acetaminophen to be sold in over-the-counter therapeu- tic preparations, but regulates other carcinogens to very low levels in the environment.

Acetaminophen or paracetamol is one of the most popular and widely used over-the-counter analgesic and antipyretic drugs in the world. Physi- cians in the United States routinely recommend acetaminophen for use by children and adults as a safe alternative to products containing aspirin or aspirin-analogues. In recent years, however, studies have reported on the genotoxic and carcinogenic effects of this compound. Although acetaminophen does not cause gene mutations, there is clear evidence that it causes chromosomal damage in mammalian cells. This suggests that acetamino- phen may have a similar effect *in vivo*, an effect supported by studies demon- strating increased incidence of liver and bladder tumors in mice and rats. Regardless, health professionals generally consider acetaminophen safe for human use. This is because the therapeutic dose for acetaminophen is much smaller than the threshold dose for genotoxic and carcinogenic effects.

Acetaminophen is a threshold carcinogen. For adults, the recom- mended therapeutic dose of acetaminophen in over-the-counter preparations is generally less than 1000 milligrams (mg), taken as often as 4-times a day (Tylenol PM). Assuming an adult body weight of 70 kg (US EPA 1996), administering the maximum amount of an over-the-counter preparation containing acetaminophen can result in a dose that exceeds 57 mg per kilogram (kg) of body weight (bw) per day (57 mg/kg/day). In contrast, doses of up to 300 mg/kg-bw/day in the rat and 1000 mg/kg-bw/day in the mouse do not cause cancer. In fact, even higher doses of acetaminophen in animal studies and in clinical cases of human overdose are most often associated with liver toxicity and not endpoints of cancer. Physicians and scientists take this as evidence that acetaminophen is safe for therapeutic use in humans. In contrast, the US EPA tends to ignore such low-dose-no- effect evidence for threshold carcinogens, using a linear low-dose non-thresh- old model to extrapolate to very low doses to regulate their allowable level in the environment. The assumption inherent in the use of this model is that a single molecule can cause cancer. The US EPA typically uses this model to extrapolate down to a compound concentration corresponding to a risk of one additional cancer in one million people. For threshold carcinogens, this level may be much lower than the threshold for cancer.

In this presentation, the carcinogenic potency (CSF) of acetaminophen is estimated using the linear low-dose non-threshold model typically employed by the US EPA. This CSF is compared to US EPA derived values for other threshold and non-threshold carcinogens. The results of this analysis suggest that the US EPA's use of the low-dose linear model for estimating the cancer potency of threshold carcinogens is flawed. In summary, there seems to be an inconsistency in the evaluation and regulation of carcinogenic compounds. This inconsistency allows acetaminophen to be sold in over-the-counter therapeutic preparations, but regulates other threshold carcinogens to very low levels in the environment.

Acetaminophen, Dose-Response Assessment, Carcinogen

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