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FILE: ▪ Coumarin
▪ Safety Assessment
▪ Toxicokinetics

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RE: Safety Assessment of Coumarin

Felter SP, Vassalo JD, Carlton BD, Daston GP. A safety assessment of coumarin taking into account species-specificity of toxicokinetics. *Food Chem Toxicol*. 2006;44:462–75.

Coumarin (1,2-benzopyrene) occurs naturally in a variety of plants—such as cinnamon (*Cinnamomum verum*), lavender (*Lavandula* spp.), peppermint (*Mentha* x *piperita*), tonka beans (*Dipteryx odorata*), cassia (*C. aromaticum*), and celery (*Apium graveolens* var. *dulce*).

Coumarin is used as an additive in perfumes and fragranced consumer products at concentrations ranging from <0.5% to 6.4%. Coumarin is also used clinically as an antineoplastic agent and to treat lymphedema and venous insufficiency. Coumarin's use as a food additive was banned by the Food and Drug Administration in 1954 because of its reported hepatotoxicity in rats. Adverse effects to coumarin exposure are rare in humans; however, recent evidence indicates that coumarin exposure can cause liver tumors in mice. The objective of this study was to evaluate data on the metabolism and toxicity of coumarin and to conduct a human health risk assessment.

In humans, adverse side effects to coumarin exposure appear to be limited to high oral doses. Mild dizziness, diarrhea, and vomiting have been reported; however, the only potentially serious side effect reported was hepatotoxicity after oral doses of 50–7000 mg/d. Cessation of coumarin treatment results in the restoration of normal liver function. No alteration in liver enzymes has been reported by patients receiving coumarin dermally, i.e. topically, even after regimens lasting as long as 6 months. Apparently, the transdermal route of application circumvents the rapid first-pass liver metabolism of coumarin. Rats seem to be particularly susceptible to liver effects of ingested coumarin, whereas mice seem to be particularly sensitive to lung effects, only at high doses however. Evidence indicates that coumarin is not genotoxic (does not cause genetic mutation) and does not interact directly with DNA in target organs.

The mechanisms of toxicity to coumarin are clearly species-specific. Coumarin is rapidly eliminated after oral dosage in humans. For example, 83% of a 200-mg/kg dose was found in the urine of humans within 24 hours of administration. This finding indicates the rapid absorption of coumarin by the gut in humans. In contrast, only 35% of an equivalent dosage was found in the urine of rats after the same time period. Coumarin is not stored in tissues. In humans, the susceptibility to toxicity appears to be limited to oral clinical doses and in subpopulations with the following predisposing factors: hepatic disease, low glutathione concentrations, polymorphic glutathione-*S*-transferase and aldehyde dehydrogenase, (liver enzymes) and elevated activities of P450 enzymes CYP2E1 and CYP1A. In rats, coumarin-induced hepatotoxicity is associated with the rate-limiting detoxification of *o*-hydroxyphenylacetaldehyde (*o*-HPA). Mice are "relatively resistant" to hepatotoxicity because they are known to rapidly eliminate *o*-HPA. However, the lungs of mice are sensitive to coumarin toxicity, which is attributable to the high metabolic rate of coumarin epoxidation in Clara cells. The lungs of rats make little epoxide, and no Clara cell toxicity has been observed in this species. Likewise, human lungs do not form epoxide and it appears reasonable to conclude that humans are not susceptible to coumarin-induced lung toxicity.

No-observed-effect levels (NOELs) for noncancer and cancer effects of coumarin in the liver have been identified for various species: 42 and 16 mg/kg/day for male and female Sprague-Dawley rats, respectively; 50 mg/kg in B6C3F1 mice; diets containing 1% coumarin for 13 weeks in Syrian hamsters; 10 mg/kg in dogs; and 22.5 mg/kg/day in baboons. A NOEL for humans has not been clearly established because, despite the numerous case reports of hepatotoxicity, no clear, dose response relationship has been identified. It is important to note, however, that liver toxicity in humans has not been reported after dermal exposure to coumarin, even at therapeutic doses: The recommended oral dosage for the treatment of lymphedema is 135 mg/day initially, followed by 90 mg/day as a maintenance dosage. Doses as high as 7000 mg/day (>1000 mg/kg/day) have been well-tolerated by most patients for the treatment of cancer and chronic infections.

In summary, toxicity and carcinogenic responses to coumarin exposure are species-specific, nongenotoxic, and directly related to specific metabolism and detoxification capabilities. On the basis of observed liver effects of coumarin in rats, a safe lifetime daily exposure for humans has been calculated to be 0.64 mg/kg body weight, which is protective against both cancer and noncancer effects.

—Brenda Milot, ELS

Note: There is a difference between naturally-occurring coumarins in plants vs. dicoumarol, i.e., coumadin (warfarin), the drug used as an oral blood thinner. Coumarins (derivatives) do not apply to the subject of this article which is coumarin (a specific compound). There is no relationship to the drug, coumadin. References made by some researchers wrongly suggest that all coumarins are anticoagulant, which is clearly not the case. The coumarin in this HerbClip should not be confused with coumarin derivatives like coumadin that are potentially toxic.

The American Botanical Council has chosen not to reprint the original article.