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# Safety assessment of vitacoxib: Acute and 90-day sub-chronic oral toxicity studies

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ABSTRACT

Vitacoxib, is a newly developed coxibs NSAID (selective inhibitors of cyclooxygenase-2). To date, no experimental data have been published concerning its safety for use as an additive in the human diet. In the present study, we assessed the acute and sub-chronic toxicity of vitacoxib administered by gavage. The acute toxicity tests in Sprague Dawley (SD) rats and ICR mice demonstrated that vitacoxib at a dose of 5000 mg/kg BW failed to alter any of the parameters studied. In the 90-day sub-chronic toxicity test, vitacoxib was administered to SD rats at the doses of 0 (control), 5, 10, 20, 30, and 60 mg/kg BW. The results demonstrated that there were no significant differences for most indexes of sub-chronic toxicity throughout the experiment at the dose of 5–20 mg/kg BW, indicating no apparent dose-dependent. However, there were significant histopathology changes in the liver and kidney, and alterations in some biochemical parameters in the 60 mg/kg BW group. Based on these findings, the gavage $LD_{50}$ was determined to be > 5000 mg/kg in SD rats and ICR mice, and the 90-day gavage no-observed-adverse-effect level (NOAEL) of vitacoxib was considered to be 20 mg/kg BW under the present study conditions.


## 1. Introduction

Vitacoxib as a new compound drug in China,2-(4-chloro-5-p-tolyl-1H-imidazol-1-yl)-5-(methyl sulfonyl) pyridine ($C_{16}H_{14}ClN_3O_2S$), belongs to coxibs which are selective inhibitors of cyclooxygenase-2 (COX-2). Its structure is similar with the other analogs of this group, including celecoxib, rofecoxib and parecoxib, as shown in Fig. 1.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for the treatment of arthritis and inflammation in both human and animals (Budsberg M. S. B. S. C, 2005; Isomura et al., 2014). Selective cyclooxygenase-2 (COX-2) inhibitors contain unique class of drugs (Brune K, B. H., 2004). The coxibs are a subclass of NSAIDs designed to selectively inhibit cyclooxygenase-2 (COX-2) (Garret A et al., 2001). The action mechanism of coxibs is that COX-2 was the source of prostaglandins $E_2$ and $I_2$, which mediate inflammation, and that cyclooxygenase-1 (COX-1) was the source of the same prostaglandins in gastric epithelium, where they afford cytoprotection (Garret A et al., 2004). World widely, several coxibs drugs have been introduced to human, and others currently are under governmental review for human use (Budsberg M. S. B. S. C, 2005). The Food and Drug Administration (FDA) has approved three coxibs (e.g. celecoxib, rofecoxib and valdecoxib). Meanwhile, etoricoxib has been approved for marketing by European regulatory authority (Garret A et al., 2004). However, the clinical trials revealed that COX-2 inhibitors were associated with the increased risk for cardiovascular events, with some drugs of the class having worse risks than others. In this regard, two coxibs were withdrawn from the market. Rofecoxib has been withdrawn from the market by Merk (Garret A et al., 2004). Besides, lumiracoxib has been withdrawn from the market in several countries, mostly due to its potential for causing liver failure (sometimes requiring liver transplantation). It

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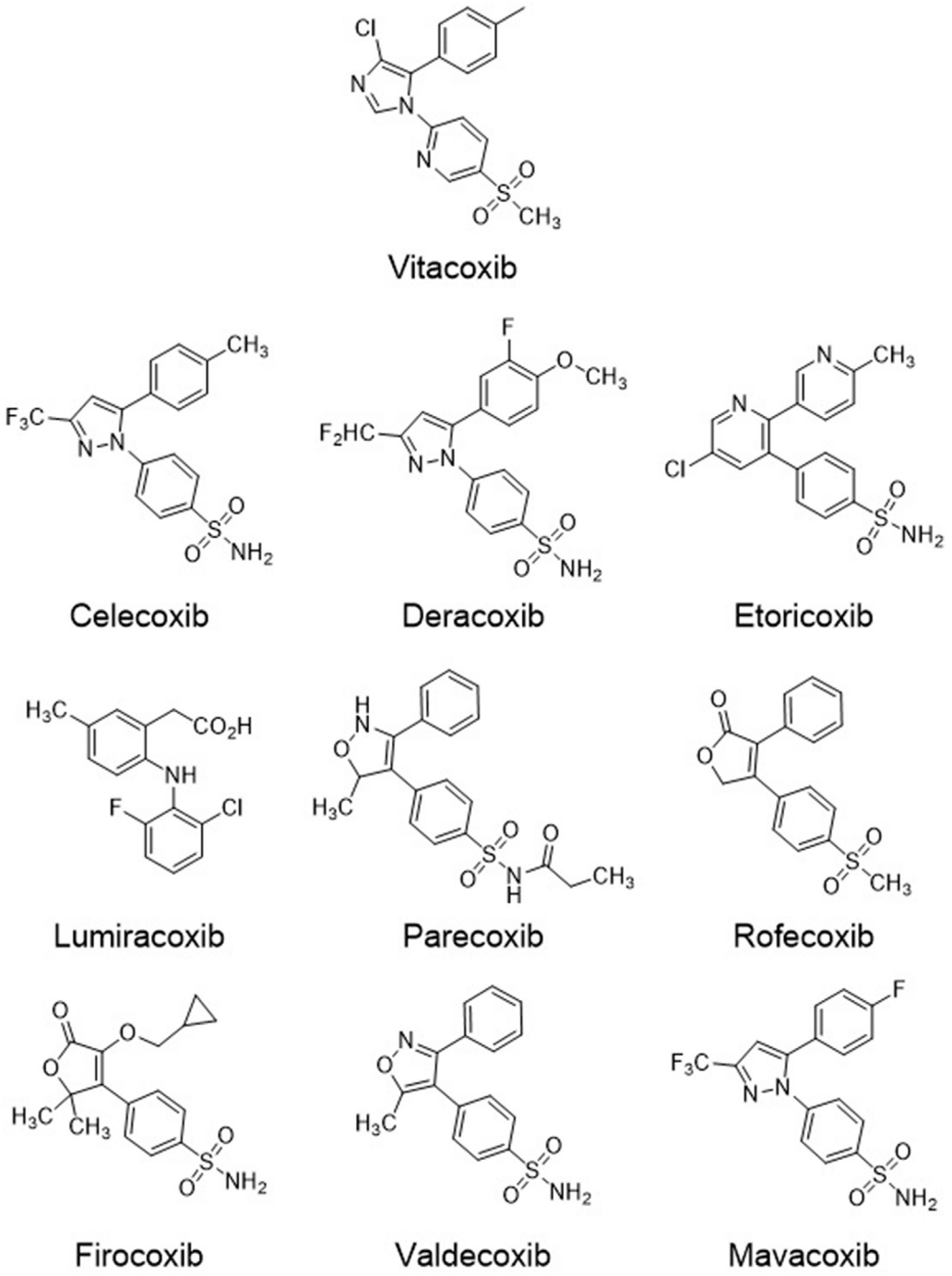


**Fig. 1.** Biochemical structure of the coxib NSAIDs.

is still sold in a few countries, including Mexico, Ecuador and the Dominican Republic, as the trade name of Prexige (sometimes misquoted as "Prestige"), but it has never been approved by FDA (Shaojun, 2008).

Despite its widely use, the research of new drugs in this class, and their effects such as gastrointestinal (GI) irritation, renal and hepatic toxicity, interference with hemostasis, and reproductive problems persist (Budsberg M. S. B. S. C, 2005). Several approved COX-1-sparing veterinary medicines are available, such as meloxicam, etodolac, and carprofen, but only a few coxibs have been approved, including deracoxib (as "Deramaxx" in Novartis) which was approval by FDA in August 2002, and firocoxib which was approved by FDA in 2007 (Wilson J.E., 2004; Kay et al., 2000; McCann M.E., et al., 2005). Mavacoxib (Trocoxil™) was approved by European Union for the treatment of pain and inflammation (Cox et al., 2010).

Vitacoxib, as a new anti-inflammatory drug, is developed by Beijing Orbiepharm Co., Ltd for the treatment of pain and inflammation in dogs. Vitacoxib, a selective COX-2 inhibitor, demonstrates excellent anti-inflammatory and analgesic activity both in vitro and in vivo models tested and could be a more viable candidate than the existing celecoxib (Yan et al., 2013). However, the acute, sub-