Comment

Is Phenylbutazone a Genotoxic Carcinogen? A Weight-of-Evidence Assessment

Robert D. Combes
Independent Consultant, Norwich, UK

Summary — Published in silico, in vitro, in vivo laboratory animal and human data, together with information on biotransformation and data from structure–activity analyses with two decision-tree systems (ACToR and Toxtree), have been used in a weight-of-evidence (WoE) assessment to determine whether phenylbutazone (PBZ) is a genotoxic or a non-genotoxic carcinogen. This was undertaken to facilitate the risk assessment of human exposure to this veterinary drug via the consumption of horsemeat from treated animals. Despite problems with data interpretation at all tiers of the database, it was concluded that PBZ behaves like a genotoxic carcinogen with a threshold dose. This conclusion is based mainly on the results of a definitive rodent bioassay, and on the following observations: a) that PBZ has weak in vitro activity only at high concentrations in some genotoxicity assays, accompanied by high levels of cytotoxicity; b) that it (and a major metabolite) is able to cause sister chromatid exchanges in vivo in rodents; and c) that it can induce cytogenetic effects in vivo in humans. It also takes into account the known and predicted activities of the parent drug, some of its metabolites and two structural analogues, and, importantly, several of the drug’s other biochemical effects that are unrelated to toxicity. However, this conclusion is not fully supported by all the evidence, and much of the information is based on old papers. Therefore, more studies are required to establish whether the concentration thresholds seen in vitro would translate to dose thresholds for carcinogenicity, such that a safe dose-level could be defined for the purposes of assessing risk. It was disappointing that a WoE approach to evaluating all of the available hazard data, as is increasingly being advocated to improve the hazard identification paradigm, was unable to provide definitive answers in this case, particularly in view of the large numbers of animals that had been used to provide much of the information.

Key words: ACToR, carcinogenicity, decision-tree systems, genotoxicity, horsemeat, phenylbutazone, risk assessment, threshold dose, Toxtree, weight-of-evidence.

Address for correspondence: Robert Combes, c/o FRAME, Russell and Burch House, 96–98 North Sherwood Street, Nottingham NG1 4EE, UK.
E-mail: robert_combes3@yahoo.co.uk

Introduction

This paper has two aims: a) to determine whether the veterinary drug, phenylbutazone (PBZ), is a genotoxic or a non-genotoxic carcinogen by assessing the published literature; and b) in so doing, to evaluate the ability of a weight-of-evidence (WoE) approach to hazard assessment to provide useful information for estimating the risk of carcinogenesis from human exposure to PBZ.

The second objective was prompted by the fact that there is increasing pressure to use a WoE assessment, involving a holistic consideration of human hazard, based on information from in silico, in vitro, in vivo and human studies. This pressure is in response to legislation calling for more chemicals testing, the failure of the traditional preclinical safety testing paradigm, with its emphasis on laboratory animal data to accelerate the successful introduction of new drugs into clinical practice, and advances in computational predictive toxicology (1–4).

PBZ was selected, because traces of the drug could contaminate horsemeat that has recently been found to have entered the food chain in the UK, masquerading as beef (5). In addition, in silico, in vitro, in vivo and human data are available, which show various effects, including rodent carcinogenicity, but discrepant genotoxicity data. The availability of clinical genotoxicity information for a drug that has been shown to be a rodent carcinogen is rare. Therefore, the database for PBZ is suitable for a WoE assessment, as it includes information for each major tier of an integrated testing strategy that could have been applied