

REGULATORY TOXICOLOGY

POSITION PAPER

Subject :
BENDIOCARB

CONTENTS :
Response to CLH dossier
for bendiocarb TC

Date : 12/09/2014

Introduction

In the Proposal for Harmonised Classification and Labelling from January 2014, UK CRD proposes that bendiocarb be classified under CLP as follows:

CLP: Acute Tox 2: H300, Acute Tox 2: H330, Acute Tox 3: H311

This paper will summarize the data available on which the classifications are based for oral and inhalation toxicity, and the position of the comment submitter regarding the classification proposed by UK CRD.

Acute oral toxicity

Four studies conducted in the rat, and two studies conducted in the mouse, were relied upon for the estimation of acute oral toxicity. The LD₅₀ values from these studies are listed below in increasing order; as multiple batches were tested in some studies, there may be multiple entries from some studies.

Table 1. Oral LD₅₀ values in the male and female rat.

Sex	Vehicle	LD ₅₀ value, mg/kg bw	Study
M	Corn oil	25.0	(CAR: Document A90517 6.1.1/02)
		40	(CAR: Document A90942 6.1.1/04)
	45		
	Glycerol formal	45	(CAR: Document A90940 6.1.1/03)
		48	(CAR: Document A90942 6.1.1/04)
		54	
		57	
		64	
		0.5% gum tragacanth	71.9
	107.6		
	110.1		
	120.8		
	135.3		
	152.3		
F	Corn oil	27.3	(CAR: Document A90517 6.1.1/02)
		34	(CAR: Document A90940 6.1.1/03)
	Glycerol formal	40	

Table 2. Oral LD₅₀ values in the male and female mouse.

Sex	Vehicle	LD ₅₀ value, mg/kg bw	Study
M	0.5% gum tragacanth	28.3	(CAR : Document A90477 6.1.1/05)
F	0.5% gum tragacanth	28.2	(CAR : Document A90477 6.1.1/05)
	Glycerol formal	45	(CAR: Document A90940 6.1.1/03)

From these data it is clear that there is a range of acute oral toxicity values from which to choose for the classification of bendiocarb. Acute oral toxicity from the hamster, rabbit, and cat are also reported, but are not considered in this document.

According to Version 4.0 (November 2013) of the Guidance on the Application of the CLP Criteria,

Where several experimentally determined ATE values ... are available, expert judgement needs to be used to choose the most appropriate value for classification purposes. Each study needs to be assessed for its suitability in terms of study quality and reliability, and also for its relevance to the substance in question in terms of technical specification and physical form. Studies not considered suitable on reliability or other grounds should not be used for classification.

In general, classification is based on the lowest ATE value available i.e. the lowest ATE in the most sensitive appropriate species tested. However, expert judgement may allow another ATE value to be used in preference, provided this can be supported by a robust justification. If there is information available to inform on species relevance, then the studies conducted in the species most relevant for humans should normally be given precedence over the studies in other species. If there is a wide range of ATE values from the same species, it may be informative to consider the studies collectively, to understand possible reasons for the different results obtained. This would include consideration of factors such as the animal strains used, the experimental protocols, the purity of the substance and form or phase in which it was tested (e.g. the particle size distribution of any dusts or mists tested), as well as exposure mode and numerous technical factors in inhalation studies. This assessment may aid selection of the most appropriate study on which to base the classification.

If there are different LD₅₀ values from tests using different vehicles (e.g. water vs. corn oil or neat substance vs. corn oil), generally the lowest valid value would be the basis for classification. It is not considered appropriate to combine or average the available ATE values. The studies may not be equivalent (in terms of experimental design such as protocol, purity of material tested, species of animal used, etc.) making such a collation or combination unsound.

Based on the above paragraphs, in the first instance classification would be based on the data obtained in CAR: Document A90517 6.1.1/02, showing an LD₅₀ after oral administration of 25.0 mg/kg bw in male rats, and 27.3 mg/kg bw in female rats. However, in this study bendiocarb was suspended in corn oil, which is known to increase the bioavailability of substances and to lead to increased plasma levels of bioactive compounds. It is the position of the comment submitter that this study overestimates the toxicity of bendiocarb through artificially increasing its oral absorption. This is supported by the decreased latency to death observed in CAR: Document A90517 6.1.1/02, in which

the earliest deaths occurred at 7 minutes after administration of the compound. In nearly all other treated studies, deaths first occurred after 12-14 minutes.

Conversely, suspension of bendiocarb in 0.5% aqueous gum tragacanth (CAR: Document A90464 6.1.1/01) led to marked decreases in acute oral toxicity of bendiocarb, as well as to a substantially increased latency to mortality in some treatment groups (greater than 18 hours in some cases). Given the difference between the results obtained in CAR: Document A90464 6.1.1/01 using gum tragacanth and those obtained in either CAR: Document A90517 6.1.1/02 or CAR: Document A90942 6.1.1/04 using corn oil and glycerol formal respectively, the results observed with gum tragacanth are probably less relevance to the classification for acute oral toxicity of bendiocarb.

If only the values obtained using glycerol formal are considered, the LD₅₀ values range from 40 to 64 mg/kg bw in the male rat on the basis of 7 trials in two studies (CAR: Document A90940 6.1.1/03 and CAR: Document A90942 6.1.1/04), and from 34 to 40 in the female rat on the basis of two trials (CAR: Document A90940 6.1.1/03).

Although in the criteria for classification and labelling quoted above, the combination or averaging of ATE values is not generally considered appropriate due to potential differences in experimental design, it is the position of the comment submitter that the values resulting from CAR: Document A90942 6.1.1/04 can in fact be averaged. In this study, the acute oral toxicity of five batches of technical active ingredient were tested in the male rat. Based on the batch numbers cited, these batches were produced consecutively and can be assumed to be highly similar. The clinical signs reported in all five trials were similar, and in general the latency to death was similar across all trials.

The toxicity of bendiocarb to the female rat has only been tested in two trials conducted with glycerol formal and are similar to those obtained in the male rat. However, in the absence of additional trials, it is difficult to say whether the values of 34 and 40 mg/kg bw/day would be fully representative of the toxicity of bendiocarb to females. As more data is available from males, only the males should be used for estimation of acute oral toxicity.

Thus, if the studies using corn oil and gum tragacanth are set aside for reasons of artificially increased or decreased bioavailability respectively, and the five values in the male rat from CAR: Document A90942 6.1.1/04 are averaged to determine the acute oral toxicity of bendiocarb, this results in an average LD₅₀ value of 52 mg/kg bw and a classification of bendiocarb in Acute Tox Category 3; H301, Toxic if swallowed for acute oral toxicity. In accordance with DSD criteria, classification with T, R25 can be considered appropriate, as proposed by UK CRD.

Acute inhalation toxicity

Only one inhalation toxicity study was conducted with bendiocarb (CAR: Document A90617 6.1.3/01). In this study, animals were exposed to concentrations of 0, 0.248, 0.377, 0.512, and 0.701 mg/L for four hours via whole-body exposure. Mortality at the various concentrations of bendiocarb is shown below.

Table 3. Mortality in male and female rats following acute (4-hour) inhalation to bendiocarb.

Concentration, mg/L	Mortality in males, %	Mortality in females, %
0	0	0
0.248	0	0
0.377	0	20
0.512	40	40
0.701	60	100

As this was a whole-body exposure study, these animals were likely exposed via both inhalation and oral routes, and this study cannot wholly be relied upon for an estimation of inhalation toxicity alone. If the study had been conducted via nose-only inhalation methods, it is certain that the derived LC₅₀ would have been greater than that observed here.

It is therefore the position of the comment submitter that bendiocarb should be classified for acute inhalation toxicity on the basis of the results from the males, 0.61 mg/L. This would result in classification under CLP as Acute Tox Category 3; H331, Toxic if inhaled. In accordance with DSD criteria, classification with T, R23 can be considered appropriate, as proposed by UK CRD.

Summary

For acute oral toxicity of bendiocarb, it is the position of the comment submitter that the most relevant study for classification is CAR: Document A90942 6.1.1/04, and furthermore that the mean of these values obtained in the male rat can be used for classification.

For acute inhalation toxicity, it is our position that, as the inhalation study was whole-body rather than nose-only, the values obtained almost certainly reflect both inhalation and oral exposure; thus, the LC₅₀ obtained in the males (0.61 mg/L) should be used in order to avoid penalizing the substance for greater exposure than actually calculated through use of the LC₅₀ from female rats (0.47 mg/L).

Based on these arguments, it is the position of the comment submitter that the appropriate classification for bendiocarb is:

CLP: Acute Tox 3; H301, Acute Tox 3; H331, Acute Tox 3; H311