Comment on the classification of MES as acute dermal toxicity category 3 (refer to CLH Report 10.2)

Introduction

The evaluating CA suggested that Mecetronium ethyl sulphate (MES) should be classified for acute dermal toxicity in category 3 (Acute Tox. 3, H311 – Toxic in contact with skin). The applicant is of the opinion to reject a classification for acute dermal toxicity in category 3 as inappropriate and applies for classification for acute dermal toxicity not exceeding category 4 (Acute Tox. 4, H312 – Harmful in contact with skin).

Justification to apply classification for acute dermal toxicity in category 4

It is suggested by the evaluating CA that Mecetronium ethyl sulphate (MES) should be classified for acute dermal toxicity in category 3 (Acute Tox. 3, H311 – Toxic in contact with skin). The proposal is based on an acute dermal toxicity test that was performed as a limit test with 2000 mg/kg test substance according to OECD Guideline 402. The test substance was MES as manufactured for the use in biocidal products and contained 30% MES resulting in an LC_{50} of > 600 mg/kg bw for the pure active substance. However, at this point it seems scientifically not justified to use the derived value of > 600 mg/kg bw for classification.

Thus, the applicant would like to argue against a classification for acute dermal toxicity in category 3 based on a limit test performed with a diluted compound, which poses here a major problem.

A prove for non-classification or classification in category 4 will require a new animal test for acute dermal toxicity. However, from results on skin corrosion/irritation studies it is deduced that the pure active substance has corrosive properties. It is proposed to classify MES as skin corrosive in subcategory 1C (Skin Corr. 1C). According to Guidance on the Biocidal Products Regulation Volume III: Human Health Part A: Information Requirements, an acute dermal toxicity study does not generally need to be conducted if the substance is classified as corrosive to the skin. Therefore, an acute toxicity study for the dermal route with the pure active substance is not acceptable regarding the animal welfare concept.

Nevertheless, acute dermal toxicity can be estimated from the available tests:

a) In the limit test for acute dermal toxicity only long-lasting irritant effects were observed; in some animals, these effects were not completely reversible after 14 days. The exposure did not reveal any systemic effects. MES is not known to exhibit a specific acute toxic mode of action. In the dermal acute toxicity study no mortality and no clinical signs were observed at all while irritant effects were determined at the application site. An absence of any clinical sign indicates the absence of any systemic effect upon dermal exposure. All available information including acute toxicity studies and studies on toxicity upon repeated dose application determined local effects at the site of contact. Whereas systemic effects or

relevant clinical signs related to systemic effect of toxicity were not determined. Overall, only local effects were reported as relevant toxic effect for the substance. Therefore, toxic effects upon dermal exposure are limited by the irritant effects on skin and covered by classification as Skin Corr. 1C.

b) In the ADME study 14C-labelled MES was applied dermally for 24 h. Less than 3% of the radioactivity were recovered in urine, faeces, cage washings during the sampling period of 72 h and radioactivity in tissues at termination indicating a minimal absorption of the radiolabelled test substance. From this study a dermal absorption of less than 3 % was determined and systemic exposure is considered as very low.

c) Moreover, in oral studies with single and repeated exposure the predominant effects of MES were local effects at the site of first contact indicating a low systemic toxicity of MES. The toxicity of the test substance is due to local effects on the mucous membranes in the gastro-intestinal tract even in repeated-dose toxicity studies.

Additional animal study to avoid Acute Toxicity Cat. 3, H311 – Toxic in contact with skin

An additional animal study for acute dermal toxicity to prove that the LC_{50} after dermal application is considerably higher than 600 mg/kg and meets at least the cut-off value for Acute Tox. 4 or even for non-classification is not preferable for the following reasons:

- The active substance MES is manufactured as 29% solution. The manufacturing process results in an aqueous solution containing 29% MES. Anhydrous active substance is not produced by the manufacturing process. The acute dermal toxicity test must be performed with the specified MES quality. A Limit Test with 5000 mg/kg body weight (MES 29%) would be the only option to achieve a better result in acute dermal toxicity testing, but the feasibility due to the high amount of test material is questionable.

- From results on skin corrosion/irritation studies it is deduced that the pure active substance has corrosive properties. It is proposed to classify MES as skin corrosive in subcategory 1C (Skin Corr. 1C). In the acute dermal toxicity study 30% MES provoked long-lasting irritant effects. The performance of an additional acute dermal toxicity study in rat is therefore considered unacceptable due to animal protection reasons.

- The local effects after dermal application of MES are covered by the classification as skin corrosive, subcategory 1C. An additional acute dermal toxicity study would not provide any additional scientific information.

Summary

The applicant proposes to reject a classification for acute dermal toxicity in category 3 as inappropriate. The local effects after application of MES are covered by the classification as skin corrosive (Skin Corr. 1C). Systemic effects are not expected. An additional acute dermal toxicity study to avoid classification is regarded as unacceptable due to the corrosive properties of MES. The applicant therefore applies for a classification for acute dermal toxicity not exceeding category 4.