

## Comments to the CLH report on pyridate

### Hazardous to the aquatic environment:

We agree with the proposal of the CHL report.

### STOT:

**STOT SE 1:** The proposal to classify with STOT SE 1 is supported based on the data in the CLH report. It was noted, however, that in one of the position papers from the applicant (Kobel W, 2012) included as an annex to the CLH report, it is stated (p. 151) that 'potentially relevant observations were (...) not seen in the initial phases of the repeat dose gavage studies in rats and dogs'. The onset of clinical signs in dogs after a single dose should be confirmed in the study reports.

**STOT RE 2:** Additional classification also with STOT RE 2 may be considered based on the following observations in the dog studies:

- 1) It appears from the clinical signs in dogs in relation to acute effects (table 16 in the CLH report) compared with the long-term effects (table 50 in the CLH report) that the clinical signs of neurotoxicity are more severe at the same dose after repeated dosing in both 90-d dog studies (see data highlighted in yellow below).
- 2) A mild exacerbation of clinical signs may also be reflected in the experts proposal of a combined NOAEL of 60 mg/kg bw per day for acute effects in the 90-day dog studies and on a combined NOAEL of 40 mg/kg bw per day for repeated dose effects in the 90-day dog studies.
- 3) In one of the position papers from the applicant (Kobel W, 2010) included as an annex to the CLH report, it is stated (p. 148) that 'In the first subchronic study, emesis, ataxia, opisthotonus, hypoactivity, salivation, mydriasis, nystagmus, head swing, muscle fasciculations, rarely also head tilt were noted at 200, less at 60 mg/kg. Onset was 1 – 3 h after dosing, returning to normal within 24 hours up to 19 days. Recovery thereafter was not always complete.

It should be mentioned that the above considerations regarding classification were made under the assumption that the rat-specific guidance values for STOT classification are to be used for dogs without allometric scaling.

90-d dog study, clinical signs (Tomkins, 1987)

Table 16 (single exposure)

≥ 60 mg/kg bw: Emesis

≥ 200 mg/kg bw: Ataxia,

hypoactivity,

opisthotonus, muscle fasciculations, head

swing, nystagmus,

mydriasis, salivation

Table 50 (repeated exposure)

≥ 60 mg/kg bw/d: Clinical signs

(emesis, salivation, ataxia,

mydriasis, nystagmus)

90-d dog study, clinical signs (Vandaele, 1990)

Table 16 (single exposure)

≥ 80 mg/kg bw:

Underactivity (F)

≥ 120 mg/kg bw: Ataxia,  
emesis, opisthotonus

Table 50 (repeated exposure)

≥ 80 mg/kg bw/d: Clinical signs  
(salivation, ataxia, hunched  
posture, emesis, pupils dilated,  
head shaking, underactivity),  
erythrocyte parameters,  
Heinz bodies, relative liver  
and kidney weight,  
histopathological changes in the  
liver (pigmentation in Kupffer  
cells)

≥ 120 mg/kg bw/d: bw gain  
(F), clinical signs  
(opisthotonus, tremor,  
prostration), HB, changes in  
organ weight and haematology,  
myelin digestion chambers