5 February 2016

Comments of Endura S.p.A. on: 10.3 Acute toxicity - inhalation route

CLH report on

tetramethrin (ISO); (1,3-dioxo-1,3,4,5,6,7-hexahydro-2H-isoindol-2-yl)methyl 2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropanecarboxylate

CLH proposal:	Acute Tox. 4, H332
Endura S.p.A. proposal:	No classification
Reference:	Venugopala RK, 2006, Toxicology Department, Advinus Therapeutics Private Limited., Endura Study N° 4414/05
Technical deficiencies:	Volume of air chamber 500 L, suggesting long time to achieve steady-state of concentration; no indication of whether concentration measurements performed in breathing zone; dense aerosol accumulation in chamber of G2 groups. Absence of signs of acute neurotoxicity in comparison to other studies suggests that concentration of 5.63 mg/L may not have been achieved in the breathing zone, study not appropriate for classification purposes
Comment of Endura S.p.A.:	The chamber was allowed to attain the equilibrium for at least 30 minutes (see the table below) and the sampling for concentration in the chamber air was taken at 45 minutes after the start of the exposure. The exposure was started at 11:25 AM for G2 group (as per raw data):

Sample for AI (replicates) G2 group- from breathing zone	Sampling time		Duration of sampling (min)	Analysed concentration (mg/l of air)
	Start time	End time		
Sample 1	12:10 pm	12:20 pm	10	5.7938
Sample 2	01:10 pm	01:20 pm	10	5.0949
Sample 3	02:10 pm	02:20 pm	10	4.7697
Sample 4	03:05 pm	03:15 pm	10	6.8685
Mean ±SD				5.63 ± 0.86

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Based on the above results of Tetramethrin (mg/L of chamber air) collected from the breathing zone, it is evident that the chamber air concentration of the test item was constant throughout the exposure period indicating the steady state of concentration.

As indicated in the report, the presence of dense aerosol inside the chamber during exposure period had obscured the visibility of the rats for clinical sign evaluation. The occurrence or absence of clinical signs during that period can therefore not be ascertained.

The study must be considered fully valid with an LC50 > 5.63 mg/L and cannot be disregarded for classification. Tetramethrin should not be classified for inhalation toxicity.

Reference: Suzuki T, Kohda H, Misaki Y, Okuno Y, Koyama Y, Miyamoto J, 1981, Sumitomo Report No. IT-10-0144

Comment of Endura S.p.A.: Endura does not know this study in detail but would like to remark that whole-body exposure will always lead to oral uptake by grooming in addition to what is absorbed via inhalation. The contribution from the oral route cannot be quantified, but it will lead to stronger clinical responses, especially during long exposure periods. The study done at Advinus featured a more sophisticated technology (head only).

The whole-body exposure study should therefore be disregarded for classification.

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