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Epsilon-Metofluthrin: Comments on the CLH Report

Background:

Exponent International Ltd submits on behalf of Sumitomo Chemical (UK) PLC, the following comments on the CLH Report (May 2015) for epsilon-metofluthrin.

Comments

Report section	Report wording	Comment
1.3: Labelling (p8)	Hazard statement H302: Harmful if swallowed	Sumitomo Chemical agrees H302. The CLH report however argues Acute Tox 3 (H301: Toxic if swallowed).
2.2 Short summary of the proposal (p9)	"mortalities were observed in 7/20 rats at the top dose of 100 mg/kg"	The statement represents the selective use of data. Within this same study report: - a range-finding study under the same dosing conditions, caused no mortality in 10 (0/10) rats at this dose. Under similar dosing conditions that were closely contemporaneous, in the same test facility and same study report, mortality at 100 mg/kg bw was therefore 7/**30**. Furthermore, 4 of the 7 decedents were sacrificed for humane reasons. As the study was a neurotoxicity study, the decision to sacrifice was modified by the need to preserve samples for neuropathology (therefore a modified criterion to an acute oral toxicity study); and it was additionally demonstrated that affected rats at this dose might recover; - an additional 10 females were administered 100 mg/kg after the study to assess recovery, with a single mortality (1/10). Of the 40 animals dosed at 100 mg/kg bw in corn oil in this study report, there is no scientifically valid reason to conclude mortality as "7/20". Mortality is seen to be highly variable at this dose; the variability within the corn oil dosing data is not discussed.
4.2.1.2 Acute toxicity: inhalation (p19)	No information is given	A detailed description is necessary, to the same level as offered for acute oral toxicity. Sumitomo Chemical takes the view that a detailed description of time course and symptoms observed in the inhalation study (Yoshihito, 2002) show that inhalation toxicity (both symptoms and mortality) occurs more rapidly than by dosing orally in corn oil; although signs of toxicity are qualitatively similar to those obtained by oral dosing. These findings of absorption and the T_{max} being more rapid than by oral absorption contradict later speculation on toxicokinetics due to corn oil.
4.2.3 Summary and discussion of	"it is possible there are vehicle dependent	This statement is speculative. Since the inhalation study (where 100% bioavailability may be assumed) causes less lethality on a mg/kg basis but with a shorter T_{max}, a more

acute toxicity	differences in toxicokinetics that are revealing an intrinsic hazardous property”	probable reason is that corn oil is an inappropriate vehicle for the quantitative estimation of the oral ATE. The data owner has submitted separate argumentation (Exponent doc 0800265.uk0 – 4028) to support the view that corn oil is inappropriate.
4.2.3 Summary and discussion of acute toxicity (p20)	“There do not appear to be clear methodological reasons to exclude findings from the single oral exposure studies with corn oil vehicle (as it is a standard vehicle)”	Although corn oil is a standard vehicle, if it were to interfere with the toxicity in any way (e.g. impair detoxification) then the acute ATE in corn oil would not be a measure of “intrinsic” toxicity.
4.3.2 Comparison with criteria (STOT-SE, p24)	“a simple argument for classification with STOT-SE 1 could be made”	Sumitomo Chemical supports the CLH recommendation of **no classification** for STOT-SE. Findings of neurotoxicity were seen only at dose levels associated with mortality. Data for oral toxicity using a corn oil vehicle are not appropriate (in line with argument for the acute toxicity ATE) to compare with the cut-off for STOT-SE.
4.8.2 Comparison with criteria (STOT-RE): inhalation (p38)	“mortalities occurred throughout this study and are not considered to be a manifestation of the acute inhalation toxicity”	The reasoning for the conclusion “not considered to be a manifestation of acute toxicity” is not explained. There is a clear element of acute toxicity: at least 4 of the decedents died within 1 hour of the end of a daily exposure period; symptoms were most marked immediately after exposure and resolved by morning of the following day. If these mortalities can be concluded to be a manifestation of acute toxicity, classification for STOT-RE is not appropriate.
4.10.5 Comparison with criteria (Carcinogenicity, p 54)	“in this instance no classification appears to be most appropriate”	Sumitomo Chemical strongly supports the CLH recommendation of **no classification** for carcinogenicity. A Mode of Action via CAR activation is clearly shown, and is supported by a Human Relevance analysis (Yamada 2012). **No classification** is consistent with RAC Opinion precedents for Sulfoxaflor (2014) and Fenpyrazamine (2012).