CLH report Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2

Comments from Sumitomo Chemical (UK) Plc – Substance supplier of

1*R*-*trans*-Z-momfluorothrin

17th March 2015

Substance Name: 1*R*-*trans*-Z-momfluorothrin

EC Number: Not available

CAS Number: 1065124-65-3

Index Number: Not available

Contact details for dossier submitter: UK Competent Authority Chemicals Regulation Directorate, Health and Safety Executive, United Kingdom

Version number: 1

CLH Report: 1*R-trans*-Z-momfluorothrin		
Comments from Sumitomo Chemical (UK) Plc		
Section	**Text**	**Corrected text / Comment**
1.3 – Physico-chemical properties; Table 8	Dissociation constant: OECD **102**	Dissociation constant: OECD **112**
4.1.1 Non-human information	*The main metabolic pathways include ester cleavage and hydroxylation followed by glucuronidation on available* ***alcohol*** *groups.*	*The main metabolic pathways include ester cleavage and hydroxylation followed by glucuronidation on available* ***hydroxyl or carboxyl*** *groups.*
4.1.2 Human information	*Absorption was low and under current guidance,* ***6****% of the RTZ:RTE was available systemically.*	*Absorption was low and under current guidance,* ***3****% of the RTZ:RTE was available systemically.* **Comment:** Absorbed dose is only 1.01%. Only 1.56% and 1.67% are remained in the epidermis and the stratum corneum, respectively. Therefore, ca. 3% is absorbable. However it is the worst case estimation, because it contains tape strips 1 and 2.
4.1.3 Summary and discussion on toxicokinetics	*1R-trans-Z- momfluorothrin* ***is*** *rapidly absorbed with no bioaccumulation and excreted by the urinary and faecal routes.*	*1R-trans-Z-* ***and 1R-trans-E-*** *momfluorothrin* ***are*** *rapidly absorbed with no bioaccumulation and excreted by the urinary and faecal routes.*
4.9 Carcinogenicity; Table 19; p.43 (Rached 2012b)	*1500 ppm- decrease in body weight and body weight gain and increased* ***salivary*** *gland diffuse acinar hypertrophy (not adverse).*	*1500 ppm- decrease in body weight and body weight gain and increased* ***mandibular*** *gland diffuse acinar hypertrophy (not adverse).*
4.10.3 Other relevant information; *In vitro studies with rat hepatocytes*; p.47	*A statistically significant decrease in CAR mRNA (19% of negative controls) was observed in hepatocytes treated with CAR siRNA and Momflurorothrin at 100µM.*	*A statistically significant decrease in CAR mRNA (19% of negative controls) was observed in hepatocytes treated with CAR siRNA and* ***1R-trans-Z-*** *Momflurorothrin at 100µM.*
4.10.3 Other relevant information; *In vivo mechanistic studies in rats – females*; p.49	*In the cancer study, dietary exposure of female rats with approx. 180 mg/kg/day* ***S-1563*** *resulted in a small increased*	*In the cancer study, dietary exposure of female rats with approx. 180 mg/kg/day* ***1R-trans-Z-momfluorothrin***

	frequency in the incidence of hepatocellular adenoma.	*resulted in a small increased frequency in the incidence of hepatocellular adenoma.*
4.10.3 Other relevant information; Table 23 - *In vitro studies with human hepatocytes*	***S- 1563**: significant increases were seen at 100 and 500 µM (1.7 and 1.8-fold, respectively) compared with control.* (Okuda, 2013)	***1R-trans-Z- momfluorothrin**: significant increases were seen at 100 and 500 µM (1.7 and 1.8-fold, respectively) compared with control.*
4.10.3 Other relevant information; *In vitro studies with human hepatocytesi*; p.51	*For CYP2B6 mRNA, cultures of human hepatocytes were incubated for 48 hours with **S-1563** or phenobarbital. At the end of this period, the cells were harvested for mRNA, which was then reverse transcribed and subject to real time quantitative PCR. To determine replicative DNA synthesis, the hepatocytes were incubated for 48-hours in medium containing 0.5 ng/ml EGF and either phenobarbital, **S-1563** or HGF for 48 hours. BrdU was added 24 hours before assay termination and proliferation rate calculated compared to untreated controls.* *Compared to controls, CYP 2B6 mRNA was increased in a concentration dependent manner with significant increases at 100 and 500 µM **S-1563**, 1.7 and 1.8-fold respectively. Treatment with phenobarbital increased CYP2B6 mRNA levels to 4.8-fold of controls. Replicative DNA synthesis was significantly increased in human hepatocytes by 1.6- and 3.7-fold when treated with HGF (10 and 100 ng/ml). In contrast, **S-1563** and phenobarbital did not increase DNA synthesis compared to controls.*	*For CYP2B6 mRNA, cultures of human hepatocytes were incubated for 48 hours with **1R-trans-Z-momfluorothrin** or phenobarbital. At the end of this period, the cells were harvested for mRNA, which was then reverse transcribed and subject to real time quantitative PCR. To determine replicative DNA synthesis, the hepatocytes were incubated for 48-hours in medium containing 0.5 ng/ml EGF and either phenobarbital, **1R-trans-Z-momfluorothrin** or HGF for 48 hours. BrdU was added 24 hours before assay termination and proliferation rate calculated compared to untreated controls. Compared to controls, CYP 2B6 mRNA was increased in a concentration dependent manner with significant increases at 100 and 500 µM **1R-trans-Z-momfluorothrin**, 1.7 and 1.8-fold respectively. Treatment with phenobarbital increased CYP2B6 mRNA levels to 4.8-fold of controls. Replicative DNA synthesis was significantly increased in human hepatocytes by 1.6- and 3.7-fold when treated with HGF (10 and 100 ng/ml). In contrast, **1R-trans-Z-momfluorothrin** and phenobarbital did not increase DNA synthesis compared to controls.*

4.10.4 Summary and discussion of carcinogenicity	*In addition, examination by electron microscopy of liver sections from male and/or female rats given 3000 ppm **S-1563** for 1 or 2 weeks and 6000 ppm **S-1563** for 3 months in the repeat dose study*	*In addition, examination by electron microscopy of liver sections from male and/or female rats given 3000 ppm **1R-trans-Z-momfluorothrin** for 1 or 2 weeks and 6000 ppm **1R-trans-Z-momfluorothrin** for 3 months in the repeat dose study*
5.1.2.3 Simulation tests; Table 32 - Mineralisation as % Applied Radioactivity in aerobic water-sediment systems	*[acid14C] 1R-trans-E-momfluorothrin: Swiss, **15**% AR day **100***	*[acid14C] 1R-trans-E-momfluorothrin: Swiss, **27.4**% AR day **59***
5.4 Aquatic toxicity	*No ecotoxicity data is available for degradants*	**Comment:** Following ecotoxicity studies on degradants have been submitted to the CA by the Applicant: Acute toxicity of MMC and TFPA to fish, daphnia and algae, respectively (Miyamoto *et al.* 2013). Following OECD 201, OECD 202 and OECD 203.
5.4.2.2 Long-termtoxicity to aquatic invertebrates	*The lowest study 21-day NOEC was 0.5 µg/l (equating to 0.0005 mg/l) based on total body dry weight. While statistical differences were observed between the 0.5 and 1.3 µg/l treatments and controls for parental body length, these were considered not due to the test substance due to a lack of clear dose-response. The UK CA notes that the resulting NOEC (0.21 µg/l), should such effects be taken into account, would be in the same 0.0001 to 0.001 mg/l range as the quoted study NOEC for the purpose of classification.*	**Comment:** The NOEC value of 0.50 ug/L is considered appropriate, because in addition to a lack of dose-response, no effect was observed for the dry weight and the survival from 0.074 to 0.50 ug/L. Moreover, the mean total body length of 0.50 ug/L (i.e., 4.44 mm) is within the variation range of control (4.14 mm) and solvent control (4.55 mm). Therefore, the statistically significant difference observed at 0.50 ug/L for the length is not considered toxicant-related.
5.4.4 Other aquatic organisms (including sediment)	*No aquatic exposure data available.*	**Comment:** The following study has been submitted to the CA: Ricard, C. R. (2012); Toxicity Test with Sediment-Dwelling Midges (*Chironomus dilutus*) Under Static Conditions, Following OECD Guideline 218. [Sumitomo Ref: RWW0022]