Cyproconazole

Comments on the EChA Annex VI Report (Proposal for Harmonised Classification & Labelling) submitted by Ireland 2014

February 2015

Syngenta does not agree with the proposed classification of Cyproconazole for Carcinogenicity (Carc. 2 H351), Reproductive and Developmental Toxicity (Repr. 1B H360D) or Specific Target Organ Toxicity: Repeat dose (STOT-RE 2 H373) as contained in the Annex VI Report submitted by Ireland. The following comments provide additional support for this position.

STOT-RE Category 2 H373 (May cause damage to organs (liver)

A classification for STOT-RE category 2 is considered not required by Syngenta. Although it is acknowledged that the target organ in all the mammalian toxicology species is the liver and effect levels are within the 'Guidance Values' for classification, the effects reflect adaptive responses due to xenobiotic metabolism and are not of toxicological concern; thus these findings in the liver do not meet the criteria triggering STOT-RE classification. Further information to support this position is provided in a separate document.

Carcinogenicity Category 2 H351

Syngenta disagrees with the proposal for cancer classification (Category 2 H351) based on an increased incidence of liver tumours in the mouse only, due to supporting data to demonstrate a human non-relevant mode of action via CAR-activation. Since November 1997, when the final conclusion for cyproconazole on EU classification under Annex VI was reached, no new data demonstrating an increased risk of tumours from administration of cyproconazole have been generated. Therefore, the prior decision of the European Chemicals Bureau (ECB, 1997) that no classification for cancer is needed for cyproconazole is still warranted. In addition, further data have been generated, which strengthens the Mode of Action case for cyproconazole and non-relevance to humans. Syngenta disagrees with the proposal that the tumour mode of action could involve cytotoxicity (relevant to humans) and additional information is provided to support this. Further information to support this position is provided in a separate document.

Reproductive and Developmental Toxicity 1B H360D

A classification for developmental toxicity category 1B is considered not required by Syngenta. Cyproconazole is currently classified for developmental toxicity as Category 2 H361 (Annex of EU Dir 67/548 (26th ATP)) and although it is acknowledged that the second rabbit study (Muller, 1991)[1] may not have been considered as part of the data on which the current classification was agreed, this study is considered to add no significant new information. Syngenta considers that the combined data are insufficient to trigger a change to a H360D classification. Further information to support this position is provided in a separate document.

Specific comments on CLH report

Text quoted from CLH report is shown in italics.

Section 4.1 Toxicokinetics

The information provided in Section 4.1 contained a number of errors. Syngenta have provided an attachment highlighting required corrections, although it is acknowledged this has no impact on classification and labelling endpoints.

Section 4.7 Repeated dose toxicity

[1] Muller, 1991. SAN 619F – oral (gavage) teratogenicity study in the rabbit. No 252060, Syngenta file no SAN619/5393)

Although the 1 year dog is included in 'Table 15: Summary table of relevant repeated dose toxicity studies' no further information on the study (Warren et al., 1998 Chronic dog toxicity study by dietary administration to beagle dogs for one year) is included in section 4.7.1 Non-human information.

7.2 References for Toxicology and metabolism

Syngenta considers the inclusion of references to the common triazole metabolite studies (triazole alanine, triazole acetic acid and 1,2,4-triazole) or other cyproconazole specific metabolites inappropriate for the classification and labelling position for cyproconazole.

Section 4.10.3.8 In vitro mouse hepatocyte cell culture

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1.) *Treatment with 500 µM cyproconazole resulted in significant cytotoxicity, with intracellular ATP levels being reduced to 2% of control respectively.*

For in vitro assays, dose selection criteria to be considered are cytotoxicity and solubility of the test item in the final treatment mixture. To ensure acceptability of the hepatocyte cell culture studies, doses up to those that induced moderate cytotoxicity to cells were included. This is not indicative that cyproconazole operates via a cytotoxic mode of action in vivo.

Section 4.10.3.9 In vitro human hepatocyte cell culture

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1.) *Treatment with 125 and 500 µM cyproconazole resulted in significant cytotoxicity, with intracellular ATP levels being reduced to 67 and 1% of control respectively.*

For in vitro assays, dose selection criteria to be considered are cytotoxicity and solubility of the test item in the final treatment mixture. To ensure acceptability of the hepatocyte cell culture studies, doses up to those that induced moderate cytotoxicity to cells were included. This is not indicative that cyproconazole operates via a cytotoxic mode of action in vivo.

Section 4.10.3.10 Human relevance framework assessment of cyproconazole liver tumour induction in mice

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1. *Cyproconazole is cytotoxic to liver cells at high concentrations – see responses under section 4.10.3.8 and 9 above.*

4.11.2. Developmental toxicity

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Study 1: Dose-Finding Developmental toxicity Study In Wistar/HAN rats with cyproconazole. Becker, 1985a. Report No. RCC 048701. DAR Vol 3 B.6.6.2.1

The post-implantation loss data are only presented including the single dam at 48 mg/kg/day with total resorptions; when the single dam at 48 mg/kg/day with total resorptions is excluded from the calculation the % post-implantation losses were 7.8% (control), 2.1% (7.5 mg/kg/day), 24.2% (30 mg/kg/day), 55.6% (75 mg/kg/day) and 54.2% (120 mg/kg/day). Single incidences of complete resorptions within a study are not unusual and it is useful to consider the data with and without this dam.