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BELCHIM CROP PROTECTION

Comments on dossiers proposing harmonised classification and labelling of substances

Substance name: methyl N-(isopropoxycarbonyl)-L-valyl-(3RS)-3-(4-chlorophenyl)-β-alaninate; valifenalate

CAS Number: 283159-90-0

The table below contains the comments on the CLH Report of the active substance valifenalate by Belchim Crop Protection, manufacturer of the active substance.

Comment Number	General Comments / Hazard Class	Comment
1	General Comment – 10.6: Respiratory sensitisation	It is stated in the CLH Report (page 21): *No formally recognised and validated animal or in vitro tests currently exist for respiratory sensitisation.* Based on available data it is concluded that valifenalate does not indicate evidence for irritation of the respiratory tract. In the CLH Report (page 21) it is concluded that data are lacking. However, due to the lack of formally recognised and validated tests, tests for hazard class respiratory sensitisation cannot be provided. Therefore, the conclusion *Data lacking* is not correct. Please update the CLH report and remove that for Respiratory sensitisation data are lacking.
2	General Comment - 10.13: Aspiration Hazard	Aspiration hazard is not relevant for solid substances. In chapter 10.13.3 (page 59 of CLH Report) it is concluded that data are lacking. However, on the same page it is mentioned that Aspiration hazard is *Not relevant for solid substance.* Please update the CLH report and remove that for Aspiration hazard data are lacking.
3	Carcinogenicity	Belchim Crop Protection agrees with the proposal by Dossier Submitter Hungary: *Not classified*

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		There is no evidence to support a classification in category 2 based on available in-vivo studies. In the available carcinogenicity study in rats, after 104 weeks of treatment there were no valifenalate-related changes in neoplastic findings up to and including the limit dose level of 1000 mg/kg/day (NOAEL for carcinogenicity = 1000 mg/kg in both sexes). In the available carcinogenicity study in mice, there was an increased incidence of hepatocellular adenomas and carcinomas in males receiving 850 or 5000 ppm, while the hepatocellular carcinomas at 850 ppm were within historical control incidences. In female mice an increase in adenomas only was reported. Although hepatocellular tumours are relatively common in mice, a full range of investigative toxicology studies including comparison of wildtype with knock-out mice has been performed to clarify the mode of action for formation of hepatocellular tumours induced by valifenalate and to confirm the non-relevance for human. These mechanistic studies identified that valifenalate induced hepatocellular tumours in mice by a phenobarbital/peroxisome proliferation-type mode of action via CAR/PXR and PPARα nuclear receptors. This mechanism of hepatocellular tumour formation is considered as not relevant for human. Alternative modes of action including activation of alternative nuclear receptors, genotoxicity or cytotoxicity could also be excluded. Therefore, Belchim Crop Protection agrees with the conclusion of the dossier submitter Hungary that valifenalate does not meet the classification criteria for carcinogenicity under CLP.
4	Mutagenicity	In line with the results of the available studies, Belchim Crop Protection agrees with the proposal by Dossier Submitter Hungary: *Not classified*
5	Reproductive toxicity	In line with the results of the available studies, Belchim Crop Protection agrees with the proposal by Dossier Submitter Hungary: *Not classified*
6	Physical hazards	Some parameters are not evaluated and have been reported as data lacking in CLH Report for valifenalate (compare Table 6, page 4). These parameters are no data requirement under Regulation (EU) 1107/2009 and therefore no data are

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		lacking. Further argumentation and the reason of non-relevance is provided for the respective hazard classes. <u>Substances which in contact with water emit flammable gases</u> • Valifenalate does not interact with water to become spontaneously flammable nor does it give off flammable gases in dangerous quantities. Therefore, no data lacking. <u>Self-reactive substances</u> • Valifenalate is not a thermally unstable substance and is not liable to undergo a strongly exothermic decomposition even without participation of oxygen (air). Valifenalate is not explosive, an organic peroxide nor is it oxidising. Therefore, no data lacking. <u>Pyrophoric solids</u> • Valifenalate, even in small quantities, is not liable to ignite within five minutes after coming into contact with air. Therefore, no data lacking. <u>Organic peroxides</u> • Not to evaluate and not applicable as valifenalate is not a peroxide. Therefore, no data lacking. Valifenalate has no physical hazards for classification. For some hazard classes lacking data is mentioned in CLH report. However, these data are no requirement for active substance regulated under Regulation (EU) 1107/2009. Therefore, no data are lacking. Additionally, the explanation provided above confirms that even without specific data no classification for these hazard classes is required. Belchim Crop Protection kindly ask to update the CLH report accordingly and kindly asks to replace for the above-mentioned points *Data lacking* by *Not classified*.
7	Acute toxicity	In line with the results of the available studies, Belchim Crop Protection agrees with the proposal by Dossier Submitter Hungary: *Not classified*

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8	Skin corrosion/irritation, Serious damage/eye irritation and Skin sensitisation	In line with the results of the available studies, Belchim Crop Protection agrees with the proposal by Dossier Submitter Hungary: *Not classified*
9	Specific target organ toxicity – single/repeated exposure	In line with the results of the available studies, Belchim Crop Protection agrees with the proposal by Dossier Submitter Hungary: *Not classified*
10	Hazardous to the aquatic environment	In line with the results of the available studies, Belchim Crop Protection agrees with the classification proposed by Dossier Submitter Hungary: *Aquatic Category 2*
11	Hazardous for the ozone layer	In line with the results of the available studies, Belchim Crop Protection agrees with the proposal by Dossier Submitter Hungary: *Not classified*