COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in this table as submitted by the webform. Please note that the comments displayed below may have been accompanied by attachments which are not published in this table.

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Substance name: bupirimate (ISO); 5-butyl-2-ethylamino-6-methylpyrimidin-4-yl dimethylsulphamate
CAS number: 41483-43-6
EC number: 255-391-2
Dossier submitter:

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
13.08.2013	France		MemberState	1
Comment received				
FR agrees with the classification proposal for the human health and the environment.				
Dossier Submitter's Response				

Date	Country	Organisation	Type of Organisation	Comment number
09.08.2013	Germany		MemberState	2
Comment received				
The German CA supports to establish a harmonised classification and labelling for Bupirimate, which is an active ingredient in plant protection products.				
Dossier Submitter's Response				

Date	Country	Organisation	Type of Organisation	Comment number
05.08.2013	Belgium		MemberState	3
Comment received				
We would you like to thanks Netherlands for the CLH report on Bupirimate.				
Dossier Submitter's Response				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
16.08.2013	United Kingdom		MemberState	4
Comment received				
We agree that the thyroid tumours are probably not relevant for human health, but perhaps more consideration could be given in the discussion section to the alternative mode of mode of action proposed in the Ashby paper				
Dossier Submitter's Response				

Date	Country	Organisation	Type of Organisation	Comment number
26.07.2013	Spain		MemberState	5

Comment received

p 56. Summary and discussion of Carcinogenicity
The dossier submitter proposes a classification of Bupirimate under DSD and CLP classification criteria as Carc. Cat. 3, R40 (Limited evidence of a carcinogenic effect), and as Carc. 2, H351 (Suspected of causing cancer). The Spanish CA, after a detailed review of all available data, does not agree with this proposal.
In a 24-month study in Sprague Dawley rats (Ben- Dyke et al., 1976a, 1977a), an increase in the incidence of neoplastic lesions in thyroid, mammary glands and skin was observed. However, this increase in the incidence of neoplasms is not considered sufficient evidence to classify Bupirimate regarding its carcinogenicity potential due to the following reasons:
1) An increase in the incidence (12.5%) of mammary gland adenocarcinomas was observed in females at 769 mg/kg bw/d. These neoplastic lesions are malignant tumours, however they were not statistically significant and they were within the range of the contemporary historical control data (0-13.3%) of the testing in laboratory (Huntingdon Life Sciences; 1973-1979). Besides, these tumours are common in female Sprague-Dawley rats [Guidance on the Application of the CLP Criteria, section 3.6.2.6.2. NTP (2005)].
2) A statistically significant increase in the incidence of thyroid follicular adenoma was observed in males at 729 mg/kg bw/d (27.5%). Historical controls of this incidence were not reported in the DAR. However historical control data of follicular adenoma in thyroid is available in the open literature. Baldrick (2005) and Charles River (2004) compiled historical controls of 13 carcinogenicity studies (1991-2002) and 31 long-term studies (1991-2002) respectively. The incidence of these tumors was out of the range of historical controls provided by Baldrick (0-9.1%) and Charles River (2-12%). This increased incidence occurred only with benign tumours. Besides, in a thyroid function study (Ashby, 1979) performed with Bupirimate, prolonged disturbances in the hypothalamus-pituitary-thyroid (HPT) axis were seen. A decrease in thyroxin (T4) levels in blood plasma, morphological changes in the thyroid indicatives of hypothyroidism, and a greater demand for iodine uptake were observed. Increased thyroid weight occurred at dose levels similar to the dose inducing thyroid tumours in rats (450 mg/kg bw/d). Following the ECB recommendations (ECBI/49/99-Add.1 Rev.2) when a non-genotoxic substance produces a low/medium potency perturbation of the thyroid-pituitary axis the mechanism of action is not relevant for humans.
3) The incidence of subcutaneous fibromas at the highest dose in female rat (12.5%) was statistically significant. However this increase was low and only slightly above the contemporary historical controls (0-9%). Besides, there was not a clear dose-response relationship and this incidence was within the historical control range (0-15%) compiled in the open literature (Baldrick, 2005). In this scientific article, Baldrick stated that skin fibromas are benign and common tumours in Sprague-Dawley rat.
4) These were only neoplastic lesions in one species (rat), but not in dog and mouse.
5) Bupirimate is considered a non-genotoxic agent. The mechanism behind tumour formation in the rat is not genotoxic.
The Spanish CA considers the available information does not provide enough evidence to support a classification of Bupirimate for carcinogenicity.

References:
Carcinogenicity Evaluation: Comparison of Tumor Data from Dual Control Groups in the Sprague-Dawley Rat (Baldrick P., 2005).
Compilation of Spontaneous Neoplastic Lesions and Survival in Crl:CD (SD) Rats from Control Groups (Charles River Laboratories, 2004)

Dossier Submitter's Response

Date	Country	Organisation	Type of Organisation	Comment number
05.08.2013	Belgium		MemberState	6
Comment received				
We support the classification Carcinogen Category 2 due to the limited evidence observed in one single species: statistically increased incidence of skin fibroma in female rats. In this same study, follicular adenomas in the thyroid are observed, however these tumors are not relevant for human, as bupirimate induce a disturbance in the hypothalamus-pituitary-thyroid axis, and a hyperactivity of this axis can lead to these tumors in rats. An increase in mammary adenocarcinoma is observed in female rats, however it is not statistically significant and it is within the historical control data, then not relevant for the classification.				
Dossier Submitter's Response				

Date	Country	Organisation	Type of Organisation	Comment number
14.08.2013	Netherlands	Makhtehsim Agan Holding B.V., The Netherlands, on behalf of Maktheshim Chemical Works Ltd.	Company-Manufacter	7
Comment received				
classification with R40 is not considered appropriate - please see attached explanation				
Dossier Submitter's Response				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
05.08.2013	Belgium		MemberState	8
Comment received				
For eye irritation, we acknowledge that few data are available and no classification is supported.				
Dossier Submitter's Response				

OTHER HAZARDS AND ENDPOINTS – Skin Senzitation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
26.07.2013	Spain		MemberState	9

Comment received
p. 29 Summary and discussion of sensitisation The Spanish CA supports the proposed classification of Bupirimate as skin sensitizer; R43 (May cause sensitisation by skin contact) according to Directive 67/548/EC and as Skin Sens. 1B, H317 (May cause an allergic skin reaction) according to Regulation (EC) 1272/2008 based on the Netherlands reasoning.
Dossier Submitter's Response

Date	Country	Organisation	Type of Organisation	Comment number
05.08.2013	Belgium		MemberState	10
Comment received				
We support the classification for skin sensitization. The outcome of guinea pig maximization test indicate that erythema is observed in more than 30% of tested animals: - 14 out of 20 test group animals after 24H and 8 out of 20 after 48h (with 75% challenge) - 9 out of 20 test group animals after 24h and 4 out of 20 after 48h (with 30% challenge) Based on the observed results, the classification 1B is warranted.				
Dossier Submitter's Response				

Date	Country	Organisation	Type of Organisation	Comment number
14.08.2013	Netherlands	Makhtehsim Agan Holding B.V., The Netherlands, on behalf of Maktheshim Chemical Works Ltd.	Company-Manufacter	11
Comment received				
classification with R43 is not considered appropriate - please see attached explanation				
Dossier Submitter's Response				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
13.08.2013	Sweden		MemberState	12
Comment received				
Sweden supports the environmental classification of Bupirimate (CAS No 4183-43-6) as specified in the proposal. SE agrees with the rationale for classification into the proposed hazard classes and differentiations. CLP- Acute aquatic hazards The lowest available L(E)C50 value for bupirimate is 1.0-1.5 mg/L obtained in fish. In this study, no mortality was observed at 1.0 mg/L during the study period whereas all the fish died at 1.5 mg/L, suggesting that the LC50 value is greater than 1 mg/L with a steep dose-response curve. In a second study carried in fish, an LC50 value between 1.25 and 2.5 mg/L was obtained. Based on the lowest LC50 value between 1.0 and 1.5 mg/L, bupirimate does not fulfil the criteria for classification as acutely toxic to the aquatic environment.				

CLP - Aquatic chronic hazards
Bupirimate is considered not rapidly degradable. Bupirimate does not fulfil the criterion of BCF >500. The lowest NOEC of 0.10 mg/L was obtained in fish. The NOEC value of 0.10 mg/L falls within the range 0.01 < NOEC ≤ 0.1 mg/L. Being not rapidly degradable, bupirimate therefore fulfils criteria for classification as Aquatic Chronic Cat. 1 (H410) with an M-factor of 1.

Directive 67/548/EEC
Bupirimate is not readily degradable and has a BCF value above 100 L/kg. The lowest availableL(E)C50 value for bupirimate is 1.0-1.5 mg/L obtained in fish. In this study, no mortality wasobserved at 1.0 mg/L for 96-hours whereas all the fish died ad 1.5 mg/L, suggesting an LC50 valuewhich is greater than 1 mg/L with a steep dose-response curve. Being not readily degradable and based on an LC50 value between 1 and 10 mg/L, bupirimate fulfils the criteria for classification with N; R51/53.

Dossier Submitter's Response

Date	Country	Organisation	Type of Organisation	Comment number
16.08.2013	Finland		MemberState	13

Comment received

We support the proposed classification according to CLP Regulation: Aquatic Chronic 1; H410 and Chronic M-factor of 1 and classification according to Directive 67/548/EEC: N; R51/53 for Bupirimate.

Dossier Submitter's Response

Date	Country	Organisation	Type of Organisation	Comment number
16.08.2013	United Kingdom		MemberState	14

Comment received

We agree with the proposed classification. However, as a minor point, the low pKa of the substance (4.0) means it will be mostly dissociated in the waters tested on the various species (fish, Daphnia, algae) and no mention has been made of this.

Dossier Submitter's Response

Date	Country	Organisation	Type of Organisation	Comment number
05.08.2013	Belgium		MemberState	15

Comment received

Based on the results of the aquatic toxicity test on the most sensitive species (fish with 96hLC50 between 1.0 and 1.5 mg/L (nominal) and a 32dNOEC=0.1mg/L(nominal)) the fact that the substance is considered as not rapidly degradable it is justified to classify, following the classification criteria of the 2nd ATP, as Aquatic chronic 1,H410. Furthermore, the substance shows low potential to bioaccumulate (BCF =128.5).

In view of the proposed classification and toxicity band for chronic toxicity between 0.01 and 0.1 mg/l, an M-factor for chronic toxicity of 1 could be assigned,

Based on the classification and labelling criteria in accordance with dir. 67/548/EEC, Bupirimate should be classified as N,R51/53. In conclusion : we agree with the proposed environmental classification by RIVM.
Dossier Submitter's Response

Attachments received:

1. The attachment provided by Makhtehsim Agan Holding B.V., The Netherlands, on behalf of Maktheshim Chemical Works Ltd on proposed classification of bupirimate contains 4 documents:
   1_Contents of Submission.pdf
   2_overview statement.pdf
   3_statement on carcinogenicity.pdf

2. Confidential attachement provided by Makhtehsim Agan Holding B.V.:
   3_study report LLNA.pdf