Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

Bupirimate

EC number: 255-391-2
CAS number: 41483-43-6

CLH-O-0000001412-86-17/F

Adopted

6 June 2014

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BUPIRIMATE (ISO); 5-BUTYL-2-ETHYLAMINO-6-METHYLPYRIMIDIN-4-YL DIMETHYLSULPHAMATE

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 some attachments received may have been copied in the table below. The attachments received have been provided in full to the dossier submitter and RAC.

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

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				
We are happy with the agreement.				
RAC's response				
Noted.				

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				
We are happy with the agreement.				
RAC's response				
Noted.				

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				
Our pleasure.				
RAC's response				
Noted.				

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				
The Ashby paper (summarized in section 4.10.1.3) also found pathological changes in the thyroid gland in rats administered with bupirimate and suggests "the action of bupirimate on the thyroid was possibly related to a blockage of the incorporation of iodine into thyroxin, leading to a type of hypothyroid non-toxic goitre (i.e. thyroid enlargement, not resulting from inflammation or neoplasm, with a decreased hormone output). This hypothesis was supported by the clinical signs (sparse hair coat and decreased protein synthesis in the growing animal, seen as decreased weight gain and less efficient food conversion), decreased T_4 levels in blood plasma, increased iodine uptake by the thyroid and increased bodyweight-relative thyroid weight and the morphological alterations." This is actually the same mode of action discussed in section 4.8.4 (Summary and discussion of carcinogenicity) in the proposal, although the blockage of iodine incorporation is not mentioned specifically. The resulting low T_4 (thyroxin) levels stimulate TSH secretion, which stimulate thyroid gland growth. This is summarized as "disturbances in the hypothalamus – pituitary – thyroid (HPT) axis" in section 4.8.4 in the proposal. Thus, even though the wording is different, the same mode of action is meant.				
RAC's response				
The comment received by UK indicates that disturbances in the HPT-axis might depend on various specific mechanisms. The RAC opinion outlines that the available thyroid function study gives some evidence that bupirimate affects the thyroid hormone axis; however, there seems to be no convincing evidence for a specific mechanism resulting in this hormonal perturbation. Specific thyroid toxicity via liver enzyme induction has not been verified. Overall, it is the RAC's conclusion that the increased incidence of thyroid gland adenomas in male rats is not sufficient evidence for classification, mainly because there were only benign tumours, because corresponding potency was low and because there was substance-related evidence of perturbation of the pituitary-thyroid gland axis.				

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

Section 4.8.4 (Summary and discussion of Carcinogenicity) and 4.8.5 (Comparison to Criteria) in the proposal already state that the mammary gland adenocarcinomas and thyroid follicular adenomas were not found to be relevant and thus no reason for classification. Therefore points 1 and 2 of the comments above are in agreement with the proposal and not further discussed.
Response to point 3: The classification for Carc. 2, H351 (CLP) is only based on the subcutaneous fibromas. If a response is significantly different from the controls and outside the even broader range of historical controls, this indicates that the effect is not a coincidence. The absence of a very clear dose-response can very well be due to a high threshold. Since the dose spacing was a factor of 50 between the lowest and highest dose, which is more than usual in carcinogenicity studies, finding a dose response relation for a threshold effect may become difficult. The data from the Baldrick study are from a different laboratory than where the Ben-Dyke study was conducted and from a different time period (i.e. 1991-2002). They are therefore less relevant than the historical control data from Huntingdon Life Sciences (where the Ben-Dyke study was conducted) from 1973-1979.
In response to point 4, the mouse carcinogenicity study was unacceptable due to high mortality. For the remaining mice only a limited number of tissues was examined not including skin but including those suggestive of neoplasia. This reduces the likelihood of detecting skin tumours and it can therefore not be concluded whether or not bupirimate is

carcinogenic in mice. In addition, the available 2-year study in dogs is not designed for detection of tumours as it uses only 4 dogs per sex. The absence of neoplastic lesions in the mouse and dog study is therefore not a valid argument against classification in this case. In response to point 5, although we agree that bupirimate is not genotoxic, we would like to point out that non-genotoxicity is not a valid argument against classification for carcinogenicity, as there are many known non-genotoxic carcinogens.

We do agree that the data are limited, that is the reason why we have not classified for Carc 1B, but for Carc 2. The comments received do not convince us to change our classification.

RAC's response

RAC is of the opinion that a carcinogenicity classification of bupirimate is more adequate than no classification. Because there is only limited evidence for carcinogenicity the RAC proposes, along with the dossier submitter, to classify bupirimate as a Category 2 carcinogen (CLP). Reference is made to the corresponding detailed discussion of the carcinogenicity data in the final RAC opinion.

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

We are happy with the agreement on the classification and the justification for it.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
14.08.2013	Netherlands	Makhteshim 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

Makhteshim Agan Holding B.V. has attached a position paper dated November 2006 on why the substance should not be classified for carcinogenicity Category 3, R40 (limited evidence of a carcinogenic effect). The arguments in this paper had already been considered in the submitted CLH proposal and thus bring nothing new. We therefore repeat the argumentation given in the CLH proposal, in response to these old comments:

The position paper states that we based our classification for Carc.2 (CLP) on both skin

fibromas and mammary adenocarcinomas. This is incorrect, it was only based on the skin fibromas. We agree that the mammary adenocarcinomas are not relevant for classification , since the increase as observed in the top dose is not statistically significant and within the contemporary historical control range. Therefore, the mammary tumors were not discussed in the summary and discussion on carcinogenicity nor in the comparison with criteria. We will therefore not respond to any comments in the position paper concerning the mammary adenocarcinomas.

On p. 3, it is pointed out that the dog and mouse study with bupirimate did not show carcinogenicity, and neither did three (rat, mouse, and dog) studies on the metabolite ethirimol. We have considered these results in our proposal and explained in section 4.8.5. that "*The results of the carcinogenicity study with ethirimol, the main metabolite of bupirimate, did not show an increase in skin fibroma. However, this study was performed with a top dose level of 500 ppm whereas the carcinogenicity study with bupirimate used 5000 ppm as the top dose level. At 500 ppm with bupirimate also no increase in skin fibroma was observed. The results with ethirimol are therefore no justification that the increase in skin fibroma with bupirimate at 5000 ppm are a chance finding. Also, it cannot be excluded that the other main metabolite ethyl-guanidine, which is not formed from ethirimol, has a role in the increase of skin fibroma. …. The absence of similar tumours in mice and dogs is not shown as in the mice study only for 10 mice per sex a full investigation of all tissues was performed whereas for the remaining mice only a limited number of tissues was examined not including skin but including those suggestive of neoplasia. This reduces the likelihood of detecting skin tumours. This and other limitations resulted in a conclusion that the study was not acceptable. The available 2-year study in dogs is not designed for detection of tumours as it uses only 4 dogs per sex.*" These five studies therefore do not carry sufficient weight in a "weight of evidence" (p.6), to overrule the positive finding in the rat study with bupirimate.

On p.4 of the position paper it is stated that for both skin fibromas and mammary adenocarcinomas no dose-response relationship can be observed. Since the dose spacing was a factor of 50 between the lowest and highest dose, which is more than usual in carcinogenicity studies, it makes finding a dose response relation difficult for a threshold effect.

The fact "that the incidence of skin fibroma for males and the sexes combined were also within the range of the HCD [historical control data]" (p.6) is not of interest, as we have argued in section 4.8.5: "*Combining the incidence of males and females in the study and comparing this with the combined incidence in the historical controls is not an acceptable method because this could result in incorrect assessment of tumours induced through a sex specific mechanism*."

The observation "that skin fibroma is a common, spontaneous tumour found in the aging rat" should be incorporated in the historical control data and is therefore not a separate argument.

Makhteshim Agan Holding B.V. has also attached a Statement on Proposed Classification, dated August 2013 on why the substance should not be classified for carcinogenicity giving four arguments:

1. Bupirimate has been intensively investigated for genotoxicity *in vitro* and *in vivo*, and was found not to be genotoxic.

2. In total, there are carcinogenicity studies in two species for both bupirimate as well as its main metabolite ethirimol. Skin fibroma were only observed in the rat carcinogenicity study at the high dose, at low incidence within the laboratory's historical control and without any preneoplastic lesions.

3. As the report (from 1976) did unfortunately not include the historical control data *per se* but just a statement of the pathologist, historical control from the lab was retrospectively requested and underpinned with published data; the historical control data indicated at least

that the observed incidence was not uncommon at the time of study conduct. 4. The occurrence of skin fibroma is not biologically plausible, as neither molecular structure nor toxicokinetics give indications why specifically the skin should be reached upon oral administration, and no skin effects or pre-neoplastic lesions were observed in any subchronic or chronic studies with bupirimate or its main metabolite ethirimol. In response to argument 1: we agree that bupirimate should not be considered genotoxic, but this is not a reason to not classify for carcinogenicity. In response to argument 2, we repeat that the other five studies had limitations that give these studies insufficient weight to overrule the positive finding in the rat study with bupirimate (see above, or section 4.8.5 in the CLH proposal for the exact limitations). In response to argument 3, we acknowledge that skin fibromas are common lesions in aging rats, but this is incorporated in the historical control data, which were exceeded. The historical control range for skin fibroma's mentioned in the CLH dossier is 0-9% (data from 1973-1979). The new historical control range as mentioned in the position paper (HCD from Charles River Laboratories for the Sprague-Dawley rat, 2004) is 1-4%. The observed percentage in the top dose group in the rat carcinogenicity study is 12.5%, which exceeds both historical control ranges. If exceedence of the contemporary historical control data of the same laboratory are not a reason to accept a response as positive, then what is? In response to argument 4, we would like to point out that is is not specifically the skin that appears to be reached by the substance, as e.g. the thyroid is also affected, but that the skin appears to be the organ reacting mostly in terms of carcinogenicity. The mechanism behind this, explaining why the skin is the target organ, is indeed unclear, but this is very often the case for substances and is not a reason not to classify. With regard to the lack of observations of skin lesions in the subchronic or chronic studies with bupirimate we can say that that: - the reported chronic studies were actuallly the carcinogenicity studies (where lesions were actually found in the rat, and the dog and mouse studies had limitations to detect this properly) - the lack of (pre)lesions in the subchronic 90-d studies were one of the reasons to decide upon a category 2 classification for carcinogenicity, instead of category 1B. In conclusion, we see no convincing argument to change our classification.
RAC's response
RAC is of the opinion that a carcinogenicity classification of bupirimate is more adequate than no classification. Because there is only limited evidence for carcinogenicity the RAC proposed, along with the dossier submitter, to classify bupirimate as a Category 2 carcinogen (CLP). Reference is made to the corresponding detailed discussion of the carcinogenicity data in the final RAC opinion.

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				
We are happy with the agreement.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation 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				
We are happy with the agreement.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
05.08.2013	Belgium		MemberState	10
Comment received				
We support the classification for skin sensitisation. The outcome of guinea pig maximization test indicates 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				
We are happy with the agreement.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
14.08.2013	Netherlands	Makhteshim 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 the attached explanation.				
Dossier Submitter's Response				
Makhteshim Agan Holding B.V. has also attached a statement on the proposed classification, dated August 2013 on why the substance should not be classified for skin sensitisation. It is argued that the three older studies were first found to be inadequate or limited, being the reason why Makhteshim performed the LLNA study. The company does not agree that the negative LLNA test is overruled by the findings in the guinea pig maximisation test and the positive human case, because "The number of animals classified as positive responders by the study director was above the trigger of 30% for a positive response 24 h after challenge (45%), but below the trigger of 30% 48 h after challenge (20%). This quick reversion of response does not speak for a true sensitizing response; this is why the new LLNA study was performed to clarify this point." and because the single human sensitization case "has been published in 1993, which was before production site was changed to				

Makhteshim Chemical Works. The purity of the technical grade bupirimate produced today has largely increased as demonstrated in several 5-batch analyses of the technical production over years, thereby removing impurities from the technical grade material. Workers involved in the production and formulation of bupirimate at the Makhteshim Chemical Works-site are monitored routinely for adverse effects by occupational health physicians since commencement of production. No adverse local effects were observed, which leaves the single reported incidence in the literature questionable."

With regard to the GPMT test: the results mentioned by the manufacturer are those for the dose of 30% w/v buprimate. However, also 75% w/v bupirimate was dosed. The dose used for challenge should be the highest non-irritating concentration. Since bupirimate is considered not to be a skin irritant, it can be assumed that 75% is indeed a non-irritant dose and this dose should be used for interpretation of the test. With this dose, the percentage of animals that reacted positive is above 30% at 24 as well as 48 hours after patch removement (70% (14/20) and 40% (8/20), respectively) and therefore trigger classification.
If Makhteshim Agan Holding B.V. has data indicating that bupirimate is not sensitizing in humans, this should be made available to RAC, because without such data, it is not possible to conclude that the single case that is mentioned is not relevant (anymore). In addition, if there are data that indicate bupirimate used to contain an impurity that is sensitizing, this would also be helpful.

RAC's response

RAC carefully discussed and assessed the result of the GPMT compared to the negative LLNA. RAC concluded that the GPMT should be considered weakly positive and that this positive evidence from the GPMT does warrant the skin sensitisation classification of bupirimate. For further details see the RAC opinion.

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
Thank you for your support.
RAC's response
Noted

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				
Thank you for your support.				
RAC's response				
Noted				

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				
Thank you for your support and comment. <u>Bupirimate has a pKa value of 4.4 and therefore considered to be a weak acid. In response to the comment over the pKa of the substance we agree that the substance dissociates partially in water.</u> A pKa of 4.4 is found for the equilibrium, bupirimate-H^+ + H_20 ←-→ bupirimate + H_30^+. In aqueous solutions, bupirimate-H^+ is predominantly present at pH < 2.4 and bupirimate is predominantly present at pH > 6.4, while both species (bupirimate-H^+ and bupirimate) are present at in-between values, pH 2.4 – 6.4. In environmentally relevant range pH 6-9, no additional charges will occur. Although this information is useful with respect to ionising parameter (change of bioavailability with pH) of bupirimate this does not change the proposed classification of the substance.				
RAC's response				
The low pKa does not cause additional dissociation under environmentally relevant pH values and does not influence the proposed classifiction, so it was not found necessary to mention.				

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 96h LC50 between 1.0 and 1.5 mg/L (nominal) and a 32d NOEC=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 a 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				
Thank you for your support.				
RAC's response				
Noted				

Attachments received:

1. The attachment provided by Makhteshim 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 Makhteshim Agan Holding B.V.:
   4_Study report LLNA.pdf