Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Aclonifen

ECHA/RAC/ CLH-O-0000001543-79-03/A2

Adopted

14 September 2011

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

[ECHA has compiled the comments received via internet that refer to several hazard classes and entered them under each of the relevant categories/headings as comprehensive as possible. Please note that some of the comments might occur under several headings when splitting the given information is not reasonable.]

Substance name: Aclonifen
CAS number: 74070-46-5
EC number: 277-704-1

General comments

Date	Country / Person / Organisation / MSCA	Comment	Response	RAC rapporteurs comments
11/02/2011	Belgium / Denauw Frederic / MSCA	we support the environmental classification proposal by Germany : Following dir. 67/548/EC : N, R50-53 Specific concentration limits : Concentration Classification C≥0.25% N; R50-53 0.025%≤C<0.25% N; R51-53 0.0025%≤C<0.025% R52-53 Following reg. 1272/2008 : Aquatic acute 1, H400; Aquatic chronic 1, H410 M-factor =100 (0.001 < L(E)C50 ≤ 0.01) Following 3thGHS :Aquatic Acute 1, H400; Aquatic Chronic 1 Acute M-factor = 100 (0.001 < L(E)C50 ≤ 0.01) Chronic M-factor = 10 (0,001 < NOEC ≤ 0,01) Some editorial or/and minor comments: 4.1.1. Stability : hydrolysis : please indicate the DT-50 values for the different pHs tested Photolysis in water, Photolysis in soil : please specify the test guideline according to which the tests were performed 4.1.3.Summary and discussion of persistence : please refer to the CLP criterion of rapid degradation instead of ready degradation in this section 7.6 please indicate also the outcome of the simulation tests : not rapidly biodegradable	Thank you for the support. Data not available Done. We now refer to rapid degradation. Done.	Noted. 2nd ATP classification added as proposed.
24/02/2011	UK / MSCA	Page 5- proposed classification- This should state Carc Cat 3; R40 instead of Xn; R40. Page 4 – proposed labelling- safety phrases- The relevant safety phrases for the proposed additional	Aclonifen has been reviewed in the	Agreed. Agreed.

Date	Country / Person / Organisation / MSCA	Comment	Response	RAC rapporteurs comments
		classifications of Carc. Cat 3;R40 and Xi;R43 should be included in the 'proposed labelling' section. We would suggest that the safety phrases S36 'wear suitable protective clothing' and S37 'wear suitable gloves' are the most appropriate ones to cover these additional classifications. Only brief summaries of the available studies are presented in the CLH report. It would be useful if more details were presented, including quantification of observed effects (e.g. state whether an effect is significant and the magnitude of the observed effect). This is particularly important for repeat dose toxicity, carcinogenicity, reproductive toxicity and where the effects are potentially relevant for classification.	programme covered by Commission Regulation (EC) No 1490/2002. Detailed information on these studies can be found in the Draft Assessment Report.	More details have now been copied from the DAR and presented in the Background Document.
28/02/2011	Denmark / Krista Bøgebo / MSCA	Denmark agrees with the proposed classification of aclonifen as Xn;R40 and Xi;R43.	Thank you.	Noted.
01/03/2011	France / MSCA	The classification proposed in the CLH report on Aclonifen is supported.	Thank you.	Noted.
02/03/2011	Sweden / Ing-Marie Olsson / MSCA	The proposals for harmonized classification and labelling should refer to the criteria of Dir. 67/548/EEC and of Reg. (EC) No 1272/2008. Please replace references to the GHS criteria with the latter throughout the report	Done.	Noted.
03/03/2011	Portugal / Maria do Carmo / MSCA	Considering the present proposal, we agree to establish an harmonised classification & labelling for Aclonifen. The proposed Classification and Labelling fulfills the criteria established both in CLP Regulation and 67/548/EEC Directive (environment). Therefore, we support this proposal.	Thank you.	Noted.
03/03/2011	Spain / Manuel Carbo / MSCA	In general we are in agreement with the environmental classification proposal, but we have some remarks: 1) The application of the H phrases: According to CLP Regulation the application of the H400 and the H410 together are redundant, therefore the H410 alone should be applied.	Thank you. As far as labelling is concerned, we agree and only H410 is proposed. However, if a substance is classified for both acute and chronic aquatic toxicity, both Hazard statements are assigned (compare	Noted. We agree with response by dossier submitter.

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		2) The M factor proposal: Although the surrogate system is applied to assign the long term hazards categories and only one M factor is derived for acute and long term hazards, it would be useful if in the M factor proposal was added that the M factor derived is for both hazards in order to be more clear.	Article 27 of EC 1272/2008 and Tab. 4.1.6 CLP-Guidance). Hence, we maintain H400 and H410 for the classification section. We agree and a clarification is added (p. 5).	Based on the 2nd ATP, a separate M-factor has now in addition been proposed for long-term hazards.
03/03/2011	Spain / Elina Valcarce / MSCA	Spain supports the Germany proposal.	Thank you.	Noted.

Carcinogenicity

Date	Country / Person / Organisation / MSCA	Comment	Response	RAC rapporteurs comments
24/02/2011	UK / MSCA	Page 26. Summary and discussion. We agree that the data presented in the CLH report appear to support classification of aclonifen as Carc. Cat 3; R40 and Carc 2 (H351) according to DSD and CLP criteria, respectively. However, for completeness, more information should be provided, such as the incidence of tumours at each dose level and concurrent control, details on the magnitude of the effects, etc. In particular, please would you clarify the incidences of brain astrocytoma observed in all the groups in the second Wistar Rat study.	Incidences of brain astrocytoma (malignant) at 0, 20, 40, 200 and 1600 ppm were 1/60, 0/60, 1/60, 1/59, 2/60 for males and 0/60, 0/60, 0/60, 1/60, 4/60 for females.	The incidences of the brain astrocytomas, as well as some other detail information, have been copied from the DAR and presented in the Background Document.

24/02/2011	France / / Behalf of an Organisation / Industry or trade association	Please refer to the position paper "Aclonifen_ position paper on R40 classification"	See response in confidential part	The incidence of the brain tumours in female rats (6.7%) is above historical control incidence data for astrocytomas as cited by the dossier submitter in the CLH report. Moreover, Walsh et al., (Toxicol Sci 1994) indicate that the incidence of astrocytomas in Wistar rats is normally low (between 0 and 2%). Also Tucker (1997) observed in 24 studies with AP rats (which is a Wistar-*derived* strain) a maximum incidence of 5% for these tumours. Given this, and the absence of a mechanistic explanation for their formation, there is some concern for the astrocytomas, justifying classifi-cation of aclonifen as having 'limited evidence of a carcinogenic effect'.

03/03/2011	Spain / Elina Valcarce / MSCA	p. 26 Summary and discussion of carcinogenicity The Spanish CA is in agreement with the proposed classification of Aclonifen as Carc. Cat.3; R40 (Harmful; Limited evidence of a carcinogenic effect) according to Directive 67/548/EEC and as Carc. Cat.2 (H551: Suspected of causing cancer) according to Regulation EC 1272/2008. This classification is based on malignant astrocytomas found in 4/60 female brains at 1600 ppm (equivalent to 86 mg/kg p.c.) in a 2 year carcinogenicity study in rats (Wason, S., 2004). The increase was statistically significant. Besides, these tumours are very rare in control groups and the incidence was over historical control values. Besides, urinary bladder tumours (2 males and 1 female) were found at the highest dose of 7000 ppm (892-984 mg/kg bw/day) in the 80 weeks study in mice (Amyes, S.J., 1991). Due to the absence of genotoxicity and the fact that the kidney is responsible for excretion of a major part of the dose, these tumours could be attributed to the constant irritation of the bladder due to precipitation of aclonifen at high doses and the probable crystal formation. This mechanism wouldn't be relevant in humans. Crystal formation was shown in 90 day study in rats (Danger, M., 1997). However, there was no clear evidence of crystal formation in mouse. Besides, aclonifen has been shown to bind with chromatin protein from urinary bladder cells (Sagelsdorff, P., 1995), so it can not be discarded a tumour-promoting epigenetic effect. Therefore, based on the data available, the mode of action for urinary bladder tumours remain unclear, and the relevance to humans can't be ruled out.	No comment	Noted. Agreed. The urinary bladder tumours at 7000 ppm are not considered relevant for classification. There is no statistical significant increase (nor for pair-wise comparison, nor for trend), and they are probably the result of a 'high dose' effect.

Mutagenicity

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	RAC rapporteurs comments
24/02/2011	UK / MSCA	We agree that, based on the information presented in the CLH report, aclonifen does not meet the criteria for classification as a mutagen.	Thank you.	Noted.

Toxicity to reproduction

/Date	Country / Person / Organisation / MSCA	Comment	Response	RAC rapporteurs comments
24/02/2011	UK / MSCA	We agree that aclonifen does not meet the criteria for classification as a reproductive toxicant.	Thank you.	Noted.

Respiratory sensitisation

Date	Country / Person / Organisation / MSCA	Comment	Response	RAC rapporteurs comments
		No comments received		

Other hazards and endpoints

Date	Country / Person / Organisation / MSCA	Comment	Response	RAC rapporteurs comments
24/02/2011	UK / MSCA	Page 17- STOT-SE- Since aclonifen is an active substance in the meaning of Directive 91/414/EEC, all human health and environmental endpoints should be considered, in accordance with Article 36(2) of CLP. Therefore, we recommend that the new endpoint STOT-SE be addressed in the CLH proposal. Page 18- skin sensitisation- we agree that aclonifen meets the criteria for classification as Xi;R43 and Skin Sens 1 (H317) according to DSD and CLP criteria, respectively.	No specific target organ toxicity was observed in acute toxicity studies.	STOT SE has now been addressed in the opinion; there is no need for classification. Noted.
01/03/2011	France / MSCA	* Identity of the substance and physical and chemical properties P 7, point 1.2: composition of the substance: The minimum purity should be mentioned as ≥ 970 g/kg and not > 970 g/kg. * Physical hazard Page 28 - paragraph 6, point 6.1 – explosivity, 6.2 – flammability and 6.3- oxidising potential : For classification, it should be useful to give details and explanation regarding these points. Page 28 - paragraph 6, point 6.2 – flammability: Could you please give some details to be able to classify aclonifen as not flammable and not only not highly flammable.	Correct. All relevant information can be found in the draft assessment report.	Noted. All details that are available have been added in the Background Document.
02/03/2011	Sweden / Ing-Marie Olsson / MSCA	Skin sensitisation: SE supports classification of aclonifen (Cas No 74070-46-5) as a skin sensitiser according to Dir. 67/548/EEC and to Reg. (EC) No 1272/2008 (please replace the reference to GHS, see general comment above). It should be noted though that the 2nd adaptation to technical progress of the CLP is being processed and is expected to be brought into force in the near future. With this adaptation subcategorisation of sensitisers into subcategories 1A and 1B will be introduced. We suggest that this is considered in the report. For aclonifen it would mean that it is a category 1A sensitiser in case the intradermal induction dose was ≤ 1% in the study referred to.	Classification proposal followed the then current version of Regulation (EC) No 1272/2008. However, adaptation to the	We agree that, based on the 2nd ATP, aclonifen is a cat. 1A sensitiser. This proposal has now been included.

Date	Country / Person / Organisation / MSCA	Comment	Response	RAC rapporteurs comments
			future version is considered possible as concentration for intradermal induction and challenge is given in the report.	
		Environment: In general we agree with the proposed classification of Aclonifen and the M factor. In addition we have some specific comments:	Thank you for the support.	Noted.
		Biodegradation The guidance document on the application of the CLP criteria provides in Annex II, part II decision logic for assessment of biodegradation (section II.4). This decision logic identifies the key data relevant for arriving at a correct assessment of biodegradation. We appreciate that all data available on degradation of the substance have been presented and summarized, however when it comes to the decision on whether a substance is or is not ready biodegradable only the he relevant data should be referred to (see the decision logic). Therefore we propose to delete field dissipation studies as they do not provide any data on mineralization of the substance. The data set provided indicates that in water/sediment study metabolites are formed. Theoretically, if the metabolites are formed quickly enough and if data on metabolites are available to show whether or not the metabolites are classifiable; this may be used in further assessment of the biodegradation of the substance. If the metabolites are not classifiable the substance can be regarded as readily biodegradable.	Field dissipation studies are deleted. We agree to the explanation, this is conform to CLP.	OK. OK.
		Bioaccumulation We agree that the substance meets the criteria for being regarded as bioaccumulative both in accordance to DSD (BCF>100) and CLP (BCF>500). We do however not agree with the statement that the criterion of BCF>500 is applicable only to not readily biodegradable substances. Both degradation and bioaccumulation are two separate criteria and should be assessed independently. Therefore we propose to amend the text in section 4.3.3 to: Aclonifen has a log Kow of 4.37. The experimentally derived steady state BCF of 2896 and kinetic BCF of 2248 are above the trigger of 100 (criterion for bioaccumulating potential conform Directive 67/548/EEC) and also above the trigger of 500 (criterion for bioaccumulating potential conform Regulation EC 1272/2008).	We agree that degradation and bioaccumulation are separate criteria that are applied independently. Therefore, the text	Noted.

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		This comment applies also to section 7.6 on conclusion on the environmental classification and labeling. Toxicity What is the relevance of long-term sediment studies for classification? In its section 4.2.1 on scope of the aquatic classification, the guidance document on application of classification criteria states that: "For most substances, the majority of data available addresses this environmental compartment. The classification scheme is limited in scope in that it does not, as yet, include aquatic sediments, nor higher organisms at the top end of the aquatic food-chain, although these may to some extent be covered by the criteria selected". It could be argued that some short-term sediment studies may have relevance for the classification (i.e. when the exposure is waterborne and thus comparable with other aquatic studies testing).	was changed accordingly (sections 4.3.3 and 7.6). However, in section 4.1.3.2. the guidance document states: "Valid data for short- and/or long term tests on other organisms shall also be considered, provided they represent equivalent species and test endpoints [...]." Hence, we consider this as additional information.	The text in section 4.1.3.2 of the guidance (as referred to in the response by the dossier submitter) refers to other aquatic species than fish, crustacea and algae or other aquatic plants. Without any criteria for sediment, we are of the opinion that presenting this additional information in the CLH report (without any substantiation for its relevance) has no value, and therefore section 7.1.1.4 has been deleted. Furthermore, for herbicides like aclonifen it is also not expected that insect are the most sensitive species.

Date	Country / Person / Organisation / MSCA	Comment	Response	RAC rapporteurs comments
03/03/2011	Spain / Elina Valcarce / MSCA	p. 20 Summary and discussion of sensitisation The Spanish CA supports the proposed classification of Aclonifen as skin sensitizer; R43 (May cause sensitisation by skin contact) according to Directive 67/548/EC and as Skin Sens. 1 (H317: May cause an allergic skin reaction) according to Regulation EC 1272/2008. This classification is based on the maximisation method of Magnusson & Kligman results after challenge, delayed contact hypersensitivity was induced in 19/20 (95%) Guinea pigs.		Noted.

COMMENTS RECEIVED:

Bayer CorpScience document:
Aclonifen_ position paper on R40 classification. Confidential document, see Annex 1a.

Scientific publications:
J. K. Haseman et al (1990). 35. Tumor Incidences in Fischer 344 Rats: NTP Historical Data, Pathobiology of the Fisher rat, 555-564.

R. C. Sills et al (1999). Examination of Low-Incidence Brain Tumor Responses in F344 Rats Following Chemical Exposures in National Toxicology Program Carcinogenicity Studies, Toxicologic Pathology vol27 n.5, 589-599.

H. A. Solleveld, C Zurcher (1986). Neoplasms of Nervous System, Patobiology of the aging rat, 55-63.

J. A. Swenberg (1986). Brain Tumours – Problems and perspectives, Fd Chem. Toxic Vol.24 No.2, 155-158.

M. J. Tucker (1997). Nervous system, Diseases of the Wistar Rat, 217-234.