# Committee for Risk Assessment

# RAC

Annex 2

## Response to comments document (RCOM)

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

## fuberidazole

**ECHA/RAC/ CLH-O-0000001404-79-01/A2**

**Adopted**

**26 October 2010**

**COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION**

**Comments that refer to several hazard classes are entered under each of the relevant categories/headings**

**Substance name: FUBERIDAZOLE**
**CAS number: 3878-19-1**
**EC number: 223-404-0**

**General comments**

| Date | Country/ Person/Organisation/ MSCA | Comment | Response | Rapporteur's comment |
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| **22/02/2010** | **Germany / Jan Averbeck / MSAC** | Page 46<br>The German CA supports to establish a harmonised classification & labelling for Fuberidazole, which is an active ingredient in plant protection products (Dir. 91/414/EEC). | Thank you. | Noted |
| **01/03/2010** | **Poland / Authority Biuro ds Substancji i Preparatów Chemicznych** | According to the article 36 (2) of Regulation No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labeling and packaging of substances and mixtures (CLP regulation) a substance that is an active substance in the meaning of Directive 91/414/EEC shall normally be subject to harmonized classification and labelling. Because fuberidazole is a benzimidazole fungicide and was approved for Annex I of Council Directive 91/414/EEC there is a legal background for Member States to send a proposal for harmonized classification and labeling.<br>Taking into account information provided in Proposal for Harmonized Classification and Labelling we agree with the harmonized classification proposed by | Thank you. | Beyond the dossier submitter's proposal RAC recommends to additionally classify Fuberidazole for carcinogenicity (CLP Carc. 2 resp. DSD Carc. Cat. 3). For the detailed justification of this RAC proposal please refer to the background and opinion document. |

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| | | UK REACH Competent Authority. Fuberdiazole is already included in Annex VI to the CLP regulation. This substance is classified as Xn; R22 and N; R50/53. The information included in proposal sent by UK REACH Competent Authority confirm this classification. | | |
| **02/03/2010** | **Denmark / Krista Julie Bøgebo / MSCA** | We agree with the proposed classification. | Thank you . | Beyond the dossier submitter's proposal RAC recommends to additionally classify Fuberidazole for carcinogenicity (CLP Carc. 2 resp. DSD Carc. Cat. 3). For the detailed justification of this RAC proposal please refer to the background and opinion document. |
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**Carcinogenicity**

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| **22/02/2010** | **Germany / Jan Averbeck / MSAC** | Page 34<br>The German CA supports not to classify Fuberidazole for carcinogenic effects. In rats uterine tumours were observed in incidences as high as in historical controls. Hence this is probably only a chance finding. In females, benign thyroid follicular cell adenomas were detected in low incidences but nevertheless above historical controls.<br>In male mice, liver adenomas were observed in incidences above (historical) controls. Considering the liver toxicity | Thank you. | Beyond the dossier submitter's proposal RAC recommends to additionally classify Fuberidazole for carcinogenicity (CLP Carc. 2 resp. DSD Carc. Cat. 3). For the detailed justification of this RAC proposal please refer to the background and opinion document. |

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| | | observed in this study, these tumours are probably not relevant for humans.<br>Considering the occurrence in one species and one sex of benign adenoma, in low incidences and the (overall) negative results in genotoxicity studies, it is considered not necessary to classify. | | |
| **27/02/2010** | **France / Antony Fastier / National Authority** | Since the mechanism of tumour formation in the thyroid of female rats is not known, it cannot be concluded that it is not relevant for humans. Due to this uncertainties, a classification for carcinogenicity could be proposed: Carc.Cat.3 R40 or Carc.2 H351. | The MS is correct that the mechanism of action of the thyroid tumours is not known. However, the mechanism was non-genotoxic. Only benign thyroid tumours were observed, which were species and sex-specific and occurred in a low incidence. We have included additional information in the Annex VI report to illustrate the background incidence of this tumour type in rats; and to indicate that the rat thyroid appears to be far more susceptible to the induction of carcinogenic tumours than is the human thyroid. Therefore, we consider the observed tumours to be of limited or no relevance to humans and propose that classification is not necessary. | Beyond the dossier submitter's proposal RAC recommends to additionally classify Fuberidazole for carcinogenicity (CLP Carc. 2 resp. DSD Carc. Cat. 3). For the detailed justification of this RAC proposal please refer to the background and opinion document. |
| **03/03/2010** | **Sweden / Chemicals Agency (KEMI)** | Three types of tumours are detected, uterine and thyroid tumours in female rats and also liver tumours in male and female mice. Even when the tumour incidence is within the historical control range as for uterine and thyroid tumours but not for the liver tumours, the control in the study should be of more importance. Since there are three different types of tumours a classification as Carc. Cat. 3; R40 (CLP Carc. Cat. 2;H351) may be appropriate. | We shall consider each tumour type in turn.<br><br>*Uterine tumours in rats*: The incidence in the high-dose group was higher than the concurrent controls but was within historical control data from studies conducted three years either side of the fuberidazole study. Also, there was no clear dose-response in tumour induction. The available information did not provide sufficient evidence that fuberidazole had resulted in an increased tumour incidence. | Beyond the dossier submitter's proposal RAC recommends to additionally classify Fuberidazole for carcinogenicity (CLP Carc. 2 resp. DSD Carc. Cat. 3). For the detailed justification of this RAC proposal please refer to the background and opinion document.For details of justification see background document. |

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| | | | *Thyroid tumours in rats:* The incidence of benign tumour induction in females of the high-dose group was slightly higher than the concurrent controls and the historical control range. Additional information has been added to the Annex VI report to provide more information on the background incidence of this tumour type in Wistar rats; and to illustrate that the rat thyroid appears to be far more susceptible to chemically-induced follicular cell adenoma than does the human thyroid. Therefore, although no information on the mechanism of thyroid tumour formation was available, we consider the tumours to be of low or no relevance to humans.<br><br>*Liver tumours in mice*: Male NMRI mice exhibited an incidence of benign liver tumours that was slightly above that of the historical control range from two years either side of the fuberidazole study. The tumours were associated with severe hepatoxicity (necrosis), which may have been responsible for the tumour formation. The mouse liver appeared to be more sensitive to the hepatoxic effect of fuberidazole than rats and dogs; male NMRI mice have an intermediate susceptibility for spontaneous liver tumour formation. These tumours were likely to be of low or no relevance for humans.<br><br>*Conclusion*: Fuberidazole was non-genotoxic in the evaluated mutagenicity | |

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| | | | studies. There was no clear increase in the incidence of uterine tumours in rats. The tumours induced in the rat thyroid and the mouse liver were benign, of low incidence, were sex- and species-specific, and occurred in single tissues of species that are known to be more susceptible to chemically-induced carcinogenicity than are those of humans. Based on the evidence, we propose not to classify for carcinogenicity. | |
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**Mutagenicity**

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| **22/02/2010** | **Germany / Jan Averbeck / MSAC** | Page 29<br>The German CA supports not to classify Fuberidazole for mutagenic hazard. | Thank you. | Noted |
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**Toxicity to reproduction**

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| **22/02/2010** | **Germany / Jan Averbeck / MSAC** | Page 36, 40<br>The German CA supports not to classify Fuberidazole for reproductive or developmental effects. | Thank you. | Noted |
| **03/03/2010** | **Sweden / Chemicals Agency (KEMI)** | Developmental toxicity<br>Fuberidazole do not seem to inhibit the spindle proteins as structural similar compounds do but still a typical | In one rat developmental study, one incidence of microphthalima occurred in each of the low- and mid-dose groups. | RAC recommends not to classify Fuberidazole for reproductive toxicity (fertility impairment and developmental toxicity). For the detailed justification |

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| | | malformation for these compounds, microphthalmia, occurs twice, one case in resp. low and mid-dose groups. Can the occurrence of this rather rare malformation be regarded as incidental and unaffected by treatment? Dose-dependency can not be expected with rare malformations. | Microphthalmia did not occur in rabbits or in two other rat studies when fuberidazole was administered at higher doses. Whilst we acknowledge that the spontaneous incidence of microphthalmia is generally low, the strain of Wistar rat used in the study in which microphthalmia occurred (Hsd cpb:WU, 'Wuppertal') is known to be susceptible to the induction of this malformation, with reported foetal incidences of 2% and litter incidences of 20%. We do not consider that the isolated incidences in rats in one study provide sufficient evidence to support classification. | of this RAC proposal please refer to the background and opinion document. |
| | | In the two-generation study clear negative effects on pup viability and body weight gain. The effects on viability and lactation indices are more severe when the dams are mated a second time (F1B) as well as in the second generation (F1A and F2B). The reduced viability indices of the pups could not be explained by a general poor condition of the dams or not clearly associated with the reduction in the body weight gain of the pups.<br>These developmental effects justify a classification as Repr. Cat. 3; R63 (CLP Repr. Cat. 2; H361d). | The viability and lactation effects observed in the rat two-generation study were not associated with overt maternal toxicity. However, the changes were inconsistent within and between generations, and they were relatively small (sometimes within the historical control data range). For these reasons it is not considered appropriate to classify for developmental toxicity. | |
| | | A question for clarification. In the Table to the 2-generation study the control values lactation index in F1A and F1B are very low 66.0 and 31.7. Are these figures correct? No explanation for this increase in pup mortality is given. | These figures are correct. No explanation for the low lactation indices was given in the study report, but in all the groups the pup deaths occurred across litters and generally between one and two weeks of lactation. | |

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**Respiratory sensitisation**

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| **22/02/2010** | **Germany / Jan Averbeck / MSAC** | Page 19<br>The German CA supports not to classify Fuberidazole for respiratory sensitising hazard. | Thank you. | Noted |
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**Other hazards and endpoints**

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| **22/02/2010** | **Germany / Jan Averbeck / MSAC** | Page 17<br>The German CA supports to classify Fuberidazole for acute toxicity (R22, H301-H302). The oral LD50 values in rats were > 300 - 792 mg/kg bw and justifies the classification with category 4 (guidance value in CLP reg.: 300 < LD50 =< 2000 mg/kg bw) and as harmful (guidance value in DSD: 200 < LD50 =<2000 mg/kg bw).<br><br>Page 19<br>The German CA supports to classify Fuberidazole for skin sensitising properties (R43, H17). In and maximisation test Guinea pigs, 50 % to 85 % of the animals showed skin reactions upon challenge (guidance value in CLP reg. and DSD: 30 % for | Thank you.<br><br>Thank you. | Noted (acute toxicity)<br><br>Noted (skin sensitisation) |

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| | | studies with adjuvant). Even though a second study with a different design (open epicutneous test) showed no skin reactions, it is considered appropriate to classify the compound because the maximisation test is considered more rigorous and out of precautionary principles (to cope with conflicting results).<br><br>Page 25<br>The German CA supports to classify Fuberidazole for specific target toxicity (repeated exposure) (R48/22, H373). In the 1-yr study in dogs, focal fibrosis of the heart was observed at dosed of 3.6 mg/kg bw/d and above (supported by an increase of creatinine kinase). This finding is evidence of cell death in a vital organ incapable of regeneration and was noted on microscopic examination following autopsy. Even though, there were no clinical signs that indicated to a heart dysfunction, we consider this finding a severe finding. Guidance value in CLP reg. for category 2 in 90-d study: 10 < C =< 100 mg/kg bw/d (applying Haber's rule this range correlates with ~2.5 < C =< 25 mg/kg bw/d in a 1-yr study). Guidance value in DSD for "harmful" in 90-d study: 5 < C =< 50 mg/kg bw/d. Therefore, the criteria for R48/22 and H373 are fulfilled.<br><br>The German CA supports not to classify for any other toxicological | Thank you.<br><br>Noted. | RAC recommends to classify Fuberidazole for specific target organ toxicity (CLP STOT RE 2; DSD R48/22). For a detailed discussion of whether to classify with STOT RE 1 or RE 2 please refer to the background and opinion document.<br><br>Noted (any other toxicological hazards) |

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| | | hazard. | | |
| **27/02/2010** | **France / Antony Fastier / National Authority** | Since increased incidence of heart fibrosis in dog occurs at 3.6 mg/kg bw/d, level below the guidance values of 5 mg/kg bw/d (67/548/EEC) and of 10 mg/kg bw/d (1272/2008/EC), therefore the classification should be : T, R48/25 or STOT RE1 (heart), H372 | UK: The MS is correct that the heart fibrosis occurred at doses below the guidance values given in Directive 67/548/EEC and CLP. These values apply directly to effects in 90-day rat studies. The proposed classification is based on effects in a one-year dog study. In such cases, the UK's approach is to take account of the overall toxicity rather than to rigorously apply these guidance values or use allometric scaling. The cardiac fibrosis in dogs only occurred after extended (one year) exposure; shorter durations of exposure with higher doses did not cause this effect. Apart from one substance-related death, the remaining animals did not exhibit clinical signs of toxicity, and the papillary muscle fibrosis was only apparent at histopathology. For these reasons, we propose a classification of Xn; R48/22 and STOT RE 2 (heart); H373. | RAC recommends to classify Fuberidazole for specific target organ toxicity (CLP STOT RE 2; DSD R48/22). For a detailed discussion of whether to classify with STOT RE 1 or RE 2 please refer to the background and opinion document. |
| **01/03/2010** | **Poland / Authority Biuro ds Substancji i Preparatów Chemicznych** | The acute environmental classification was based on the more sensitive taxonomic group – fish. The LC50 value obtained in 96-h study for Oncorhynchus mykiss performed according OECD Guideline 203 was 0,91 mg/l. The obtained value was less than 1 mg/l – the basis to classify a substance as N; R50 according to the directive 67/548/EWG or Aquatic Acute 1; H400 according to CLP regulation. Based on the LC50 value | Thank you. | Noted (environmental classification) |

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| | | obtained for Oncorhynchus mykiss the proper value of M factor was chosen.<br>We have only remark to the environmental labelling. On the page number 44 we can see:<br>"Based on the CLP Regulation, fuberidazole should be classified<br>Aquatic Acute 1, Aquatic Chronic 1<br>With the following labeling: H400 "Very toxic to aquatic life" and H410 "Very toxic to aquatic life with long lasting effects…."<br>this text should be amended as:<br>"Based on the CLP Regulation, fuberidazole should be classified<br>Aquatic Acute 1, Aquatic Chronic 1<br>With the following labeling: H410 "Very toxic to aquatic life with long lasting effects…."<br>because according to the table 3.1 of Annex VI to the CLP Regulation, substances classified ac Aquatic Acute 1; H400 and Aquatic Chronic 1; H410 required on the label only hazard statement H410 (Very toxic to aquatic life with long lasting effects).<br>Classification of fuberidazole as skin sensitizer was based on Guinea-Pig Maximisation Test (GPMT) which was conducted according to OECD 406 method. A positive response was observed in more than 50% of tested animals. We agree that this test was chosen as a basis for classification, despite in another test fuberidazole do not show sensitizing properties, because adjuvant-type test like GPMT | The presentation of the label information is now consistent with the approach taken for other substances already discussed by the Risk Assessment Committee. | Labelling with H400 plus H410 or only with H410: According to table 3.1 of Annex VI of the CLP regulation environmental labelling of fuberidazole is only with H410. In the background document H 400 is deleted when it comes to labelling.<br><br>Noted (skin sensitisation) |

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| | | is more accurate in predicting a probable skin sensitizing effect of a substance in humans than those not employing adjuvant. | | |
| **03/03/2010** | **Sweden / Chemicals Agency (KEMI)** | We agree with the proposal to classify fuberidazole for skin sensitisation. | Thank you. | Noted |
| **03/03/2010** | **Sweden / Chemicals Agency (KEMI)** | Environmental classification:<br>We agree with the proposed classification for Fuberidazole as N;R50-53, Acute 1, Chronic 1 and the proposed Specific Concentration Limits (according to DSD) and M factor of 1 according to CLP.<br><br>Specific comments:<br>4.1.1 Stability<br>Information on aqueous photolysis is difficult to use for classification purposes (see Guidance part IV, II.2-3-9) and is generally not needed as the degradation in the environment is based on data from the simulation tests.<br><br>4.1.2.1. Biodegradation estimation.<br>A QSAR estimate of biodegradation potential is presented. Since it is unclear whether the substance meets the domain of the model, this prediction is useless. In addition this section discusses persistence which is not relevant for the classification. | Thank you.<br><br>We have included some additional text concerning the limitations of photolysis data (similar to the approach taken for Abamectin). However, we think it is relevant to retain it as part of the whole picture on degradation, and to help provide context to the interpretation of the aquatic ecotoxicity data.<br><br>We included a QSAR prediction in the spirit of improving confidence in the use of estimation methods. This information was not presented in the original DAR prepared under 91/414/EEC, and we accept that it should really have been presented using the QSAR prediction reporting format. We also accept that reference to the REACH screening criteria are not relevant. Since reliable simulation | Noted (environmental classification)<br><br>Noted (specific comments as to ecotoxicity) |

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| | | | data are available, we have deleted the text from Section 4.1.2.1. | |
| | | 4.3.1.1.<br>In this section a QSAR prediction on BCF for fish is presented. Since the substances lies in the domain of the model it seems that the model has been correctly applied. However, in order to judge how accurate the prediction is more information is needed. In this particular case, however, knowing that the log Kow of the substance is 0.78-2.51 and that the substance is metabolized it is reasonable to assume that the substance does accumulate in fish. | We included a QSAR prediction in the spirit of improving confidence in the use of estimation methods. This information was not presented in the original DAR prepared under 91/414/EEC, and we accept that it should really have been presented using the QSAR prediction reporting format. Since the log Kow is below 3 and metabolism is extensive, there is no need to present a QSAR estimate so the text has been deleted. [We have interpreted the last sentence of the comment to mean that it is assumed that the substance does NOT accumulate in fish.] | |