Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Amisulbrom (ISO); 3-(3-bromo-6-fluoro-2-methylindol-1-ylsulfonyl)-*N,N*-dimethyl-*1H*-1,2,4-triazole-1-sulfonamide

EC Number: -

CAS Number: 348635-87-0

CLH-O-0000001412-86-104/F

Adopted

10 March 2016

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON AMISULBROM (ISO); 3-(3-BROMO-6-FLUORO-2-METHYLINDOL-1-YLSULFONYL)-N,N-DIMETHYL-1H-1,2,4-TRIAZOLE-1-SULFONAMIDE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

ECHA accepts no responsibility or liability for the content of this table.

Substance name: Amisulbrom (ISO); 3-(3-bromo-6-fluoro-2-methylindol-1-ylsulfonyl)-*N,N*-dimethyl-1*H*-1,2,4-triazole-1-sulfonamide
EC number: -
CAS number: 348635-87-0
Dossier submitter: United Kingdom

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	Germany		MemberState	1
Comment received				
The German CA supports the proposed classification and labeling as Carc. 2 (H351), Aquatic acute 1 (H400), Aquatic chronic 1 (H410) and the acute and chronic M-factor of 10. In our opinion it should be considered, that there is sufficient evidence for classifying amisulbrom as reproductive toxicant cat. 2 (H361fd), see specific comment. The proposed classification as Eye irrit. 2 is not supported. We propose to classify Amisulbrom as Eye Dam. 1 (see specific comment). In the IUCLID file only a few ESR for physico-chemical properties are included. Information on the other physico-chemical endpoints is however available since the substance was evaluated within the PPP assessment program and this information is also given in the CLP report. Therefore, to be consistent regarding the provided information within the IUCLID file and the CLP report it would be desirable to include all physico-chemical information in the IUCLID file, too.				
Dossier Submitter's Response				
In relation to classification as Repr 2, see specific response to comment 10 later. In relation to classification as Eye Dam 1, see specific response to comment 17 later. The relevant information for the physcio-chemical properties is included in the CLH report and in the attachment to section 13 of the CLH report. Therefore, additional information has not been included in the ICULID.				

RAC's response
The options for classification are noted.

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2015	France		MemberState	2
Comment received				
Please note that the correct molecular formula of the substance is C13H13BrFN5O4S2 (page 11)				
Dossier Submitter's Response				
Thank you for your comments. There is a typing error in the CLH report and the correct molecular formula is as noted in the comment above.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2015	Finland		MemberState	3
Comment received				
The Finnish CA would like to thank UK for very clear and well justified CLH proposal.				
Dossier Submitter's Response				
Thank you.				
RAC's response				
Noted.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
30.07.2015	United Kingdom	Nissan Chemical Europe S.A.R.L.	Company-Manufacturer	4
Comment received				
Reference: Carc. 2; H351 - Suspected of causing cancer (section 4.10.5 pages 61-63, CLH report for Amisulbrom) Amisulbrom (NC-224) administration caused an increase in benign hepatocellular tumours at high doses in rodent studies. The relevance of the finding to man was evaluated in two ways; 1. The evaluation of liver tumours reported in rodent carcinogenicity studies with amisulbrom was carried out by an expert group (confidential Scientific Advisory Group Report T527, 2014). Lack of genotoxicity, induction at high doses only and rodent specificity associated with increased liver weights and hepatic enzyme induction in the absence of hepatocellular carcinomas, led to the conclusion that the mechanism of toxicity is threshold-mediated and similar to phenobarbital which is not relevant to human risk assessment. 2. The mechanism of action was evaluated in a study using chimeric mice with humanised liver (PXB) to determine the potential for CAR activation with subsequent hepatocyte proliferation and relevance to humans (confidential report NCI14SA-BR-390, 2015;). Amisulbrom failed to induce proliferation of human hepatocytes in the chimeric mice and the results demonstrate a mode of action similar to phenobarbital which is not a human carcinogen. The reports discussing the findings are attached. It is concluded that based on the findings				

of the two reports, the mechanism of amisulbrom carcinogenesis in rodents is not relevant to humans and therefore based on the mode of action and the dose response relationship, amisulbrom should be classified as 'not likely to be carcinogenic to humans'.
Dossier Submitter's Response
Many thanks for this additional information. We have no additional comments, but note that this information should be taken into consideration by RAC in addition to the CLH report.
RAC's response
Noted. The assessment of RAC will take into consideration the two reports provided during the PC as well.

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	Germany		MemberState	5
Comment received				
Liver tumours occur at dose levels of 496 mg/kg bw/d and above in male and female rats as well as in male mice at 98 mg/kg bw/d and above. Additionally forestomach tumours occur in female rats. While the forestomach tumours were considered to be caused by a rat specific mechanism the liver tumours were not. Hence the RMS proposal to classify amisulbrom for carcinogenicity cat 2 (H351) is supported. Detailed reasons for classification as Carc. 2: The current proposal for Carc. 2 H351 can be supported. With respect to carcinogenicity, two types of tumours were observed in 2 chronic studies with rodents: hepatocellular adenoma and carcinoma in rats (both males/females) and mice (males only), and squamous cell carcinoma and papilloma in the forestomach of female rats. According to CLP guidance, forestomach tumours in rodents following gavage of irritating or corrosive, non-mutagenic substances are considered less relevant for humans, both due to the lack of corresponding organs and the presumed direct high-dose effect on the tissue. Though the reported studies are feeding studies, the incidences of papilloma and carcinoma are observed only in females at relatively low rates (2% and 4% at mid/high dose). Thus, these tumours were considered of less relevance within the scope of this classification. In the rat study, hepatocellular adenoma and carcinoma were observed at mid and high dose levels that reached/exceeded the MTD, particularly in females (as indicated by increased mortality and a marked reduction in body weight gain). The incidence of hepatocellular carcinoma was rather low (2-4%), without a clear dose response. While high liver adenoma rates in females (48% to 56%) were observed at dose levels causing excessive toxicity, a very steep increase in adenoma incidence occurred between the low and mid dose (from 2% to 48%). Thus, the toxicological significance of the liver adenoma observed in females cannot be completely excluded despite the presence of excessive toxicity. In the mouse study, the only statistically significant neoplastic change was an increase in hepatocellular adenomas in males at doses ≥800 ppm. Hepatocellular carcinoma rates in males were relatively low (4% to 8%) with no specific dose response. Sings of excessive toxicity were observed only at the highest dose level (37% reduction in body weight gain and focal hepatocyte necrosis); at lower doses, the increase in liver adenoma rates (up to 46%) is clearly above concurrent (16%) and historical (31%) controls. Therefore, these effects are considered relevant for the current classification. Several mechanistic studies indicate that the liver tumours can be associated with induction				

of hepatic CYP enzymes. Liver toxicity/hypertrophy and cell proliferation suggest a phenobarbital-like mechanism for tumour formation. Based on a MoA/HRF concept, phenobarbital-induced rodent hepatocarcinogenesis is not considered to be a relevant mechanism for humans (Holsapple et al., 2006; Elcombe et al., 2014). An important component of MoA/HRF analysis is, however, consideration of alternative mechanisms that can lead to liver carcinogenesis (i.e., genotoxicity, oxidative stress, excessive cytotoxicity etc.). There is no evidence of genotoxicity from both in vitro and in vivo tests with amisulbrom. However, sustained liver toxicity cannot be excluded as a possible cause for tumour formation. Liver toxicity at tumourigenic doses was noted as increased γ-glutamyl transpeptidase activity, increased liver weights, and histopathological changes such as hypertrophy/midzonal hepatocyte vacuolation. Changes in the biliary system (bile duct hyperplasia, cystic degeneration, extrahepatic bile duct dilatation and portal inflammation) can also be considered as signs of hepatotoxicity.

Overall, the data available indicate a clear tumourigenic response in both sexes of one species (rat), and a less prominent response in a second species (mouse) suggesting sufficient evidence of carcinogenicity in experimental animals and possible Category 1B classification. However, considering the additional factors (discussed in the report) such as the benign nature of the tumours, excessive systemic toxicity/hepatotoxicity at tumourigenic doses, and the less clear response in the mouse study, this can lead to a decreased level of concern. Thus, the criteria for Category 2 seem to be met. A further discussion if Category 2 or no classification is more appropriate in the case of amisulbrom should include a comprehensive MoA/HRF analysis for a phenobarbital-like MoA as demonstrated in Elcombe et al., 2014 and consideration of the dose-response concordance between tumour formation and liver toxicity.

References:
Holsapple MP, Pitot HC, Cohen SM, Boobis AR, Klaunig JE, Pastoor T, Dellarco VL, Dragan YP. Mode of action in relevance of rodent liver tumors to human cancer risk. Toxicol Sci. 2006 89 (1):51-6.
Elcombe CR, Peffer RC, Wolf DC, Bailey J, Bars R, Bell D, Cattley RC, Ferguson SS, Geter D, Goetz A, Goodman JI, Hester S, Jacobs A, Omiecinski CJ, Schoeny R, Xie W, Lake BG. Mode of action and human relevance analysis for nuclear receptor-mediated liver toxicity: A case study with phenobarbital as a model constitutive androstane receptor (CAR) activator. Crit Rev Toxicol. 2014 44(1):64-82.

Dossier Submitter's Response
Many thanks for these comments. A comprehensive MOA/HRF analysis would have been useful. The applicant has now submitted new data which could have an impact on the decision betweeb Category 2 and no classification. This information should be taken into consideration by RAC in addition to the CLH report.
RAC's response
Thank you for the comments. RAC agrees that a comprehensive MoA analysis would have been useful. The new information will be taken into assessment as well.

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2015	France		MemberState	6
Comment received				
No comment. Agreed				

Dossier Submitter's Response
Thank you.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2015	Finland		MemberState	7
Comment received				
We agree with the proposed classification Carc. 2 for Amisulbrom				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Noted.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	Germany		MemberState	8
Comment received				
Considering the presented study results and the respective criteria for classification, the RMS proposal not to classify amisulbrom for mutagenicity is supported.				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Noted				

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2015	France		MemberState	9
Comment received				
No comment. Agreed.				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Noted				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	Germany		MemberState	10
Comment received				
Reduced fertility occurred at dose levels of 1300mg/kg bw/d. This was, however, associated with severely impaired body weight development. Malformations occurred at 1000mg/kg bw in 12 foetuses of 2 litters in one of three rat				

developmental toxicity studies.
Consequently it has been agreed within the EU approval procedure for amisulbrom as pesticide active substance, that classification for fertility and developmental toxicity (H361fd) is required (EFSA Journal 2014;12(4):3237).
On the other hand it has been argued by the applicant and supported by mechanistic analysis, that reduced fertility might be unspecific and secondary to body weight effects and that the high incidence of malformation in similar litters may be associated with a genetic defect.

However, the picture in the scientific literature on reduced fertility due to malnutrition is not that clear (e.g. Fleeman et al 2005 BirthDeffRes could not observe a correlation). Some of the effects (ovarian atrophy) were also observed at 240 mg/kg bw/d were reduction in bw was only very limited.
Additionally, the type of malformation (cleft palate) is consistent with malformations caused by other substances of the same class (triazole fungicides) and malformations occurred not only in one dev tox study but also at the 2 top dose levels in the multigeneration study.
Thus substance specific effects should not be excluded.

Overall the position of the RMS, that evidence for classifying amisulbrom as reproductive toxicant cat. 2 (H361fd) is not sufficient should be reconsidered.

Dossier Submitter's Response

Many thanks for your comments.

Fertility - The potential effects of amisulbrom on fertility and reproductive performance have been investigated in a guideline multigeneration study in the rat. In this study, administration of amisulbrom at the top dose level of 15000 ppm (1200-1300 mg/kg bw/d) had a clear and marked effect on reproduction in F1 females; a reduction in fertility at this dose level was shown to be female-mediated. Reduced fertility was associated with severely impaired bodyweight development (from 10% up to 40% reduction in body weight during gestation and lactation of F0 females and weaning and sexual maturation of F1 pups), reduced ovarian weight and function and associated histopathology.
A number of mechanistic studies have been performed in order to clarify the aetiology of these effects of amisulbrom on female fertility. These studies showed that amisulbrom had no specific effect on the rat ovaries during gestation and lactation. Also, no inhibitory effects were apparent on aromatase activity in young female rats. In addition, no anti-oestrogenic effect was apparent in an uterotrophic assay in young female rats. Similarly, no effects on sex hormonal levels were observed in adult male or female rats. However, prenatal and postnatal exposure to amisulbrom (at the relatively high dose of ~1700 mg/kg bw/d) of offspring up to puberty (PND 40) induced lower body weight, decreased food consumption, reduced ovary and uterus weights and ovarian atrophy. Food restriction in untreated animals during gestation, lactation and weaning up to PND 40 caused similar effects, with reduced body weights, decreased ovary and uterus weights and ovarian atrophy. Based on these findings, it can be concluded that the effects of prenatal and postnatal (up to puberty) exposure to high doses of amisulbrom on ovaries and uterus in rats are the secondary consequence of impaired nutrition and growth during development due to reduced food consumption. Similar effects were not seen in a gavage study, indicating that the observed reduced food consumption was the consequence of the bad palatability of the test substance.

Overall, therefore, it can be concluded that the effects on fertility seen in the F1 females in the rat 2-generation study at a dose level (1200-1300 mg/kg bw/d) in excess of the limit dose are the secondary consequence of impaired nutrition and growth during the early

phase of development of the ovaries. Reduced fertility was associated with severely impaired bodyweight development (from 10% up to 40% reduction in body weight during gestation and lactation of F0 females and weaning and sexual maturation of F1 pups) in this study.

This conclusion is corroborated by other feed-restriction studies in rats from the open literature. In a study by Chapin et al. (1993), food restriction of Sprague Dawley rats for 15 weeks up to GD 14 (resulting in a body weight reduction of 30%) increased the length of the estrous cycle and decreased the weight of the ovaries and the number of corpora lutea. In another study (Terry et al., 2005), food restriction of female Sprague Dawley rats for 4 weeks up to GD 7 (resulting in a body weight reduction of 29%) produced overt changes in estrous cyclicity, mating and fertility.

It should be noted that, compared to the findings of these published papers, in the amisulbrom 2-generation study, at the dose level at which reduced fertility was observed, there was a much more severely impaired bodyweight development (up to 40% reduction in body weight) which occurred not only throughout gestation, but also through lactation, weaning and sexual maturation.

Overall, there are sufficient mechanistic data and supporting evidence from the literature to conclude that the effects on fertility seen in the F1 females in the rat 2-generation study are the secondary consequence of impaired nutrition and growth during the early phase of development of the ovaries and do not arise from a specific action of amisulbrom on fertility. The dossier submitter remains of the opinion that classificatiob for fertility is not justified. Although ovarian atrophy was also seen at 240 mg/kg bw/d, this occurred in a small number of females (4 vs 0 in controls) from litters with poor body weight performance before or after weaning, which is in line with the theory of impaired nutrition. Furthermore this atrophy at 249 mg/kg bw/d did not result in impaired mating performance or fertility.

Development - A low incidence of cleft palate/chondrodystrophy was observed in the absence of maternal toxicity in a developmental toxicity study and in the presence of severe maternal toxicity in the multi-generation study. The incidence of the finding just exceeded the laboratory historical control range in the teratogenicity study, but was within the laboratory historical control range in the 2-generation study. The pattern of the finding (noted in single litters and in association with other defects) suggests a spontaneous (genetic) aetiology rather than a relation to treatment with amisulbrom. The low incidence of cleft palate/chondrodystrophy observed in the rat has been shown not to be related to treatment with amisulbrom but to arise through a genetic mechanism. Therefore, classification of amisulbrom for developmental toxicity is not warranted.

Although it is true that some other triazole fungicides show a low incidence of cleft palate, this is not consistently true.

RAC's response

Thank you for the comments and the clear option for classification. It is to be noted that the conclusions referred in the EFSA Journal do not represent a formal proposal.

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2015	France		MemberState	11
Comment received				
Page 83: Fertility: During the PRAPeR, the observed effects on body weight and food consumption in the 2-generation study were not considered severe enough to totally exclude a specific effect of amisulbrom on female fertility, suggesting that classification as Repr Cat 2, H361f "suspected of damaging fertility" may be required. Development: - Increased incidence of cleft palate has been observed in the developmental toxicity study at the highest dose level (cleft palate in 12 foetuses in 2 litters (6 per litter) vs 0 in controls) in Han Wistar rats. The incidence of this malformation is outside the laboratory HCD for this strain. No maternal toxicity was observed in that study. - Furthermore, cleft palates have also been observed in pups dying before scheduled termination in the 2-generation study performed in the same strain at the highest dose level (3 foetuses in 1 litter) and in one foetus in the next lower dose level vs 0 in controls. - Cleft palate is a malformation implying a disturbance in the process of craniofacial morphogenesis commonly observed with triazoles. For the reasons listed above, it cannot be ruled out that the increased incidence of cleft palates is treatment related and a classification as Repr Cat 2, H361d "suspected of damaging the unborn child" may be required as proposed during PRAPeR meeting.				
Dossier Submitter's Response				
Many thanks for your comments. Please see our response to comment number 10 above.				
RAC's response				
Thank you for the comments; your conclusion has been noted.				

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	Germany		MemberState	12
Comment received				
According to the CLH dossier, the relevant data are lacking to conclude on this hazard.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Agreed.				

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2015	France		MemberState	13
Comment received				
No comment. Agreed.				
Dossier Submitter's Response				
Thank you.				

RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	Germany		MemberState	14
Comment received				
Considering the presented study results after oral, dermal or inhalative exposure and the respective criteria for classification, the RMS proposal not to classify amisulbrom for acute toxicity is supported.				
Dossier Submitter's Response				
Thank you.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	Germany		MemberState	15
Comment received				
Considering the presented study results and the respective criteria for classification, the RMS proposal not to classify amisulbrom for skin corrosion or irritation is supported.				
Dossier Submitter's Response				
Thank you.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
30.07.2015	United Kingdom	Nissan Chemical Europe S.A.R.L.	Company-Manufacturer	16
Comment received				
Reference: Eye Irritant Category 2 - H319 Causes serious eye irritation (section 4.4.2. pages 21-22, CLH report for Amisulbrom) The eye irritation potential of amisulbrom (NC-224) technical has been evaluated in the context of the results from equivalent eye irritation studies with other amisulbrom-containing formulations. The mild and inconsistent nature of the erythemal response to amisulbrom was compared with the mild and fully resolving erythemal responses to two other formulations containing 20% or 50% amisulbrom. Both comparator formulations had fully resolved the erythema by 6 days and were not classified for eye irritation. The eye irritation response of amisulbrom generally shows a similar pattern of severity and resolution. Not a single animal had a conjunctival score which was maintained throughout the 21 day observation period which. The grade 1 erythema which was noted intermittently in 3/6 animals was therefore considered not to be due to amisulbrom and that treatment-related erythema was fully resolved. Therefore amisulbrom warrants no classification as an eye irritant. Please refer to the attached confidential technical comments on eye irritation document (confidential report NCI-224-H2703, 2015) and eye irritation study reports (confidential reports T20SC105, 2005 and T50WG105, 2007) for more information.				

Please refer to the following attachments:

1. T50WG105_Eye irritation rabbit
2. T527 Amisulbrom, Liver tumours SAG Report
3. T528 NCI14SA-BR-390 Mechanism study_induced liver tumour
4. KIIIA 7.1.5 Eye irritation study-rabbits T20SC105_rev
5. NCI-224-H2703 Amisulbrom, Eye irritation, Technical comments

Dossier Submitter's Response

Many thanks for this additional information. We have no additional comments, but note that this information should be taken into consideration by RAC in addition to the CLH report.

RAC's response

Thank you for the comments and the additional materials; the new information will be taken into account as well.

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	Germany		MemberState	17

Comment received

Considering the presented study results and the respective criteria for classification, the substances is considered to require classification as Serious eye damage. Since effects are persistent after 21d classification as Eye Dam. 1 should be considered.

Dossier Submitter's Response

Many thanks for your comments.

A single guideline study of amisulbrom applied to the eyes of New Zealand white rabbits resulted in the presence of grade 1 conjunctival erythema in the eyes of two rabbits from 7 days to 21 days post-treatment (but not from 3 days to 6 days post-treatment). According to the CLP criteria, if, when applied to the eye of an animal, a substance produces in at least one animal effects that have not fully reversed within an observation period of 21 days, then it may be classified as Eye Damage 1 – irreversible effects on the eye. The applicant suggested that the cause of the reoccurrence of conjunctival erythema could be due to hairs liberated through grooming entering the eye. However, it is important to note that this effect was not present in the untreated eyes and is not an affect observed generally in eye irritation experiments in rabbits. With these points in mind, a simple interpretation of the criteria could lead to classification as Eye Damage 1, or no classification at all. However, on the basis that there was irritation up until day 21 of the study but that the effects observed were mild (grade 1) and inconsistent throughout the study, classification as Eye Irritant Category 2 is considered appropriate. The issue should be discussed by RAC.

RAC's response

Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2015	France		MemberState	18

Comment received

Eye irritation (page 22)
It cannot be ruled out that conjunctival erythema is treatment-related since similar effect was not observed in the untreated eyes. As this effect was not reversible within days 7 to 21, this suggests that classification as Eye Irritant Cat1 H318 "Causes serious eye damage

» may be required.
Dossier Submitter's Response
Many thanks for your comments. Please see our response to comment number 17 above.
RAC's response
Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2015	Finland		MemberState	19
Comment received				
We agree with the proposed classification Carc. 2 for Amisulbrom Eye Irrit. 2				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	Germany		MemberState	20
Comment received				
Considering the presented study results and the criteria for classification, the RMS proposal not to classify amisulbrom for skin sensitization is supported.				
Dossier Submitter's Response				
Thank you.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	Germany		MemberState	21
Comment received				
Considering the presented study results and the respective criteria for classification, the RMS proposal not to classify amisulbrom for STOT SE is supported.				
Dossier Submitter's Response				
Thank you.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	Germany		MemberState	22
Comment received				
Considering the presented study results and the respective criteria for classification, the				

RMS proposal not to classify amisulbrom for STOT RE is supported.
Dossier Submitter's Response
Thank you.
RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Aspiration Hazard

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	Germany		MemberState	23
Comment received				
No data have been presented to conclude on this hazard.				
Dossier Submitter's Response				
Additional information can not be included in the CLH report at this stage. However, we do not propose to classify the substance for aspiration hazard.				
RAC's response				
Agreed.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	Germany		MemberState	24
Comment received				
Page 103 point 5.4.1.2 Long-term toxicity to fish: The early life stage study with Pimephales promelas for amisulbrom resulted in our opinion in relevant effects on dry weight (significant rising of 25 % in comparison to solvent control) on newly fertilized fry even at the lowest test concentration of 0.0011 mg/L and in the following concentrations (26 -30 %) too. Therefore the lowest relevant NOEC of this study should be already below the lowest concentration of 0.001 mg/L. Page 112 point 5.5 Comparison with criteria for environmental hazard: Because the early life stage study with Pimephales promelas for amisulbrom resulted in NOEC of < 0.0011 mg/L which is the lowest relevant data for chronic toxicity and no other chronic toxicity data for fish are available, the use of the surrogate approach to chronic classification with lowest acute data for fish is therefore justified.				
Dossier Submitter's Response				
We thank you for your comment. Although we had concerns over use of this chronic endpoint for fish, the apparent increase in dry weight at the lower concentrations tested (Table 32 in CLH Report) was not specifically one of them. These deviations were not highlighted as being statistically significant and we have not re-done the statistics. Irrespective of this, the hazard classification is unaffected as we have proposed to use the surrogate approach to chronic classification and agree with DE in this respect.				
RAC's response				
The adequacy of the long-term study on fish is questionable. Therefore a more convenient surrogate approach to chronic classification is proposed.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON AMISULBROM (ISO); 3-(3-BROMO-6-FLUORO-2-METHYLINDOL-1-YLSULFONYL)-N,N-DIMETHYL-1H-1,2,4-TRIAZOLE-1-SULFONAMIDE

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2015	France		MemberState	25
Comment received				
We agree with the classification proposal for environmental hazard: H400 – H 410. Regarding the chronic M factor, we agree that there is a doubt on the chronic toxicity to fish as the species tested is not the most acutely sensitive. However the acute LC50 values (Cyprinus carpio: 0.0229 mg/L and Pimephales promelas 0.0363 mg/L) do not differ significantly. The proposal for the chronic M factor of 10 could be discussed as it could be considered too conservative in the current case.				
Dossier Submitter's Response				
We thank you for your comments. The doubt over the chronic fish endpoint was not just that it was not the most acutely sensitive species, it also related to the lack of difference between the acute and chronic fish endpoints. We note that DE have also questioned other aspects of the early life stage study with *Pimephales promelas* (comment 24) and so, unless the reliability of the study is resolved, we feel that the surrogate approach and chronic M-factor proposed is not overly precautionary in this case. This could be discussed at the RAC however.				
RAC's response				
The adequacy of the long-term study on fish is questionable. Therefore a more convenient surrogate approach to chronic classification is proposed.				

CONFIDENTIAL ATTACHMENTS RECEIVED

1. **Amisulbrom (ISO) – Information provided on Eye irritation rabbit**, submitted by Nissan Chemical Europe S.A.R.L. on 20/07/2015 (please refer to comment 16) (*Not published on the ECHA website*)

2. **Amisulbrom (ISO) – Information provided on Amisulbrom, Liver tumours SAG Report** submitted by Nissan Chemical Europe S.A.R.L. on 20/07/2015 (please refer to comment 16) (*Not published on the ECHA website*)

3. **Amisulbrom (ISO) – Information provided on Mechanism study induced liver tumour** submitted by Nissan Chemical Europe S.A.R.L. on 20/07/2015 (please refer to comment 16) (*Not published on the ECHA website*)

4. **Amisulbrom (ISO) - Information provided on Eye irritation study-rabbits** submitted by Nissan Chemical Europe S.A.R.L. on 20/07/2015 (please refer to comment 16) (*Not published on the ECHA website*)

5. **Amisulbrom (ISO) - Information provided on Amisulbrom, Eye irritation, Technical comments** submitted by Nissan Chemical Europe S.A.R.L. on 20/07/2015 (please refer to comment 16) (*Not published on the ECHA website*)