Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

sodium methyl [(4-aminophenyl)sulphonyl] carbamate; sodium methyl (*EZ*)-sulfanilylcarbonimidate; asulam-sodium

EC Number: 218-953-8
CAS Number: 2302-17-2

CLH-O-0000001412-86-138/F

Adopted

6 December 2016

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON SODIUM METHYL [(4-AMINOPHENYL)SULPHONYL]CARBAMATE; SODIUM METHYL (*EZ*)-SULFANILYLCARBONIMIDATE; ASULAM-SODIUM

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.

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Substance name: sodium methyl [(4- aminophenyl)sulphonyl]carbamate; sodium methyl (*EZ*)-sulfanilylcarbonimidate; asulam-sodium
EC number: 218-953-8
CAS number: 2302-17-2
Dossier submitter: United Kingdom

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	France		MemberState	1
Comment received				
We agree with the classification and the acute and chronic M factors proposed for Environmental hazards. Test material purity: Table 1 page 5: According to the DAR of the active substance (april 2016), the minimum purity of the active substance is 876g/kg expressed on a dry weight basis.				
Dossier Submitter's Response				
Thank you for your comments. The purity should be quoted as 87.6% and not 88.6% as currently stated in the CLH report.				
RAC's response				
Noted				

Date	Country	Organisation	Type of Organisation	Comment number
20.06.2016	Spain		MemberState	2
Comment received				
The Spanish CA supports the proposal of the UK Competent Authority for harmonized classification and labelling of Asulam sodium as Skin Sens 1; H317 – May cause an allergic skin reaction.				
Dossier Submitter's Response				
Thank you for your comment.				

RAC's response
Thank you for your comment

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Belgium		MemberState	3
Comment received				
BE CA welcomes this proposal for harmonized classification and labelling. As a general comment, BE CA would like to emphasize the fact that no study quality assessment is given and the potency of the effects (significance, severity) are not enough detailed. Thus, it is not always easy to conclude on their reliability (impurity? Test guideline? GLP compliance?...) and if the study can be taken into account for classification.				
Dossier Submitter's Response				
Thank you for your comments. Whilst we have not provided a quality assessment in terms of reliability scores, we are of the opinion that sufficient information is provided to allow for a determination of quality to be made. Each study includes reference to the appropriate guideline (and any deviations from guideline if relevant), GLP status and purity as far as this information is available to us. The tested batches are considered to be equaivalent to the substance identified in section 1.2 of the report (with the amendment to the purity as outlined in response to comment 1). There are questions about the reliability of the carcinogenicity studies (due to the high level of mortality noted in all groups) and the two-generation study (due to various deviations), but these points are addressed in the CLH report (refer to section 4.10.5 and 4.11.5) and taken into account in the proposed classification.				
RAC's response				
Although there are some deviations from quidances or irregularities in some study design, or in observations in some studies they have been noted and considered, and the presented data set is considered valid for assessment and concluding on a hazard classification.				

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2016	Germany		MemberState	4
Comment received				
The German CA supports the proposed harmonised classification as Skin Sens 1, Aquatic Acute 1 and Aquatic Chronic 1 as well as the corresponding M-factors of 1.				
Dossier Submitter's Response				
Thank you for your comments.				
RAC's response				
Thank you for your comment				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
20.06.2016	Spain		MemberState	5
Comment received				
We agree with the dossier submitter that the observed incidence of phaeochromocytomas in rats and the incidence of liver adenomas and carcinomas in mice do not lead to				

classification of asulam sodium for carcinogenicity, based in the same reasoning.
Dossier Submitter's Response
Thank you for your comments.
RAC's response
Thank you for your comment

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2016	Germany		MemberState	6
Comment received				
There is insufficient evidence that asulam-sodium causes phaeochromocytomas in male rats when the study data are considered in the context of the historical control incidence and possible mechanism of toxicity (4.10.6). The thyroid effects reported were consistent, however, with the laboratory historical control range and therefore not considered treatment related (Asulam sodium- Volume 3, Annex B.6: Toxicology and Metabolism, page 54).				
Dossier Submitter's Response				
Thank you for your comments.				
RAC's response				
Thank you for your comment				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	France		MemberState	7
Comment received				
Page 40: It is agreed that the available genotoxicity data are inconclusive.				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Thank you for your comment				

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2016	Germany		MemberState	8
Comment received				
The quality of the data package is such that no clear conclusion can be drawn (4.9.6).				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Agreed. Thank you for your comment.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Belgium		MemberState	9

Comment received

According to the reduction of the fertility index in F1 (91, 97, 86 and 87 % in 0, 1000, 5000 and 25000 ppm treated groups) and F2 (83, 83, 62, 74% at 0, 1000, 5000 and 25 000 ppm) rats, as well as the significant reduction of the litter size at 5000 ppm (F1 and F2) and the reduction of the survival index at 30 days in F2, BE CA cannot exclude a concern on reprotoxicity for Asulam sodium. Furthermore, important data are lacking such as: the impact of the treatment on the mother body weights, ovaries and testis weights, the limitations of the developmental study "similar to OECD TG 141" while the deviations are provided for the study "similar to OECD TG 416" in the fertility effects assessment, ...

Dossier Submitter's Response

The two-generation study in the rat had a number of limitations as indicated in table 19 (e.g., lack of information on implantaitons) which make the findings difficult to interpret. It is considered that there were no effects on the fertility, gestation, viability or survival index in the F1 or F2 litters. The fertility index was reported to be 91, 97, 86 and 87 % in the F1 generation and 83, 83, 62 and 74% in the F2 generation at 0, 1000, 5000 and 25 000 ppm respectively. There is no dose response and the value at the top dose is not significantly different to that in controls. Survival to day 30 was reported to be 87, 91, 82 and 82% in the F2 generation at 0, 1000, 5000 and 25 000 ppm respectively. Again there is no significant difference between the value at the top dose and that in controls.

A decrease was seen in litter size in F_1 pups across all treated groups which attained statistical significance at ≥5000 ppm. However, no dose response was observed as a 5-fold increase in dose to 25000 ppm only produced a decrease in litter size from 9.6 to 9.3. Litter size was reduced across treated groups in the F2 generation but was only statistically significant in the mid-dose group and did not demonstrate a dose–response relationship. Pup body weight at birth was not affected in the F1 or F2 generation.

The CLH report notes that there were no effects on reproductive organ weights or macroscopic findings in these organs in parental animals or offspring in this study and that repeat dose studies in the rat, mouse and dog did not record any alterations in reproductive organs. Further the parental body weights are reported in a table included within table 19.

The CLH report notes that in the F0 parents, top dose males had a slightly lower mean body weight compared with controls but this was not statistically significant and no dose response was observed. Body weights were affected in females only in F1 parents at the top dose and a reduced body weight gain at mating (10%) was reported.

Further to this, there were no effects on the later stages of reproduction (including post-implantation loss, resorptions or a decrease in viable foetuses) in the developmental studies. This supports the fact that the decreased litter size in the two-generation study was a chance finding. However, the limitations of the two-generation study make it difficult to fully interpret these findings.

RAC's response

The explanation provided by Dossier Submitter is supported by RAC

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2016	Germany		MemberState	10
Comment received				
There are no data (4.6.2).				
Dossier Submitter's Response				
There are no data on respiratory sensitisation.				
RAC's response				
Agree, there are no data				

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2016	Germany		MemberState	11
Comment received				
There are no data (4.6.2).				
Dossier Submitter's Response				
There are no data on respiratory sensitisation.				
RAC's response				
Agree, there are no data				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2016	Germany		MemberState	12
Comment received				
Data do not support a classification (4.2.4).				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2016	Germany		MemberState	13
Comment received				
There is no sufficient evidence for classification (4.4.1.4; 4.5.4).				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Agree, thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2016	Germany		MemberState	14
Comment received				
Data do not support a classification (4.4).				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Agree, thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	France		MemberState	15
Comment received				
Page: 26 The proposed classification "Skin sensitisation category 1; H317 May cause an allergic skin reaction" is agreed. Since the available data effectively do not permit sub-categorisation, it cannot be concluded that Asulam is a low potency skin sensitiser as it is mentioned in paragraph 4.6.1.4.				
Dossier Submitter's Response				
Thank you for your comments. The available data fit the criteria for a moderate potency skin sensitiser (60% response with a 5% intradermal induction concentration). However, as noted in the proposal, we agree there is insufficient information to inform on responses at lower induction concentraitons and to permit sub-categorisation. Therefore classification in Category 1 is proposed.				
RAC's response				
Thank you for your comment. RAC considers that subcategorisation of classification to assign cat 1B is not possible due to lack of data on incidence of skin sensitisation at lower induction concentrations. There are no data to exclude the possibility that in the Guinea Pig Maximisation Test asulam sodium at concentration of 1% will sensitise 60% of animals. It is not probable, but if such an incidence of sensitised animals would occur, the Skin Sens. 1A classification would be justified. In the current Guidance on the Application of CLP Criteria (point 3.4.2.2.2) it is noted that classification into sub-categories is only allowed if data are sufficient.				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Belgium		MemberState	16
Comment received				
BE CA agrees to classify Asulam sodium as Skin Sens. 1 considering the dermal reactions (grade 1 and 2 erythema) in 12/20 and 9/20 at 24 and 48-h, respectively, in the group challenged with a 50% Asulam sodium solution in distilled water.				
Dossier Submitter's Response				
Thank you for your comments.				
RAC's response				
Thank you for your comment. RAC considers that subcategorisation of classification to assign cat 1B is not possible due to lack of data on incidence of skin sensitisation at lower induction concentrations. There are no data to exclude the possibility that in the Guinea				

Pig Maximisation Test asulam sodium at concentration of 1% will sensitise 60% of animals. It is not probable, but if such an incidence of sensitised animals would occur, the Skin Sens. 1A classification would be justified. In the current Guidance on the Application of CLP Criteria (point 3.4.2.2.2) it is noted that classification into sub-categories is only allowed if data are sufficient.

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2016	Germany		MemberState	17
Comment received				
A classification of skin sensitisation into category 1 is supported (4.6.1.5).				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Thank you for your comment. RAC considers that subcategorisation of classification to assign cat 1B is not possible due to lack of data on incidence of skin sensitisation at lower induction concentrations. There are no data to exclude the possibility that in the Guinea Pig Maximisation Test asulam sodium at concentration of 1% will sensitise 60% of animals. It is not probable, but if such an incidence of sensitised animals would occur, the Skin Sens. 1A classification would be justified. In the current Guidance on the Application of CLP Criteria (point 3.4.2.2.2) it is noted that classification into sub-categories is only allowed if data are sufficient.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2016	Germany		MemberState	18
Comment received				
There is no sufficient evidence for classification (4.3.2).				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Agree. Thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Belgium		MemberState	19
Comment received				
Some effects on the red blood cells seem to be recurrent, possibly showing anemia in tested animals. Indeed, this effect appears often at very high doses, exceeding regulatory values. Nonetheless, according to the available data, a repeated toxic effects cannot be excluded.				
Dossier Submitter's Response				
Thank you for your comments. It is noted that haematological changes and effects on red blood cell parameters were observed in a number of the available repeated dose studies. However, these findings only occurred at dose levels in excess of the guidance				

values for classification. Therefore, whilst an effect following repeated dosing cannot be excluded, the criteria for classification with STOT-RE are not met.
RAC's response
Thank you for your comment. The effects ocurr only at exposure levels above the guidance values in the CLP Regulation.

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2016	Germany		MemberState	20
Comment received				
There is no sufficient evidence for classification (4.8.2).				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Thank you for your comment. The effects ocurr only at exposure levels above the guidance values in the CLP Regulation.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Belgium		MemberState	21
Comment received				
Based on the results of the aquatic toxicity test on the most sensitive species : Lemna Giba with 14dErC50=0.16 mg/l,and Pseudokirchneriella subcapitata with a 72hNOErC=0.02mg/l, the fact that the substance is considered as not rapidly degradable it is justified to classify, following the classification criteria of the regulation 1272/2008, as Aquatic acute 1, H400, aquatic chronic 1, H410 . . The key study for acute aquatic toxicity with Lemna gibba performed according to US EPA/FIFRA 122 and 123-2 determined a 14d ErC50. Following OECD TG 221 growth inhibition on Lemna sp is terminated after 7 days. The 7dErC50 was not calculated but 6d and 9d ErC50 are in the same range as 14dErC50. Furthermore, the substance shows low potential to bioaccumulate In view of the proposed classification and toxicity band for acute toxicity between 1 mg/l and 0.1 mg/l, an M-factor for acute toxicity of 1 could be assigned and an M-factor for chronic toxicity of 1 (not rapidly degradable substance and NOEC between 0.1 mg/l and 0.01mg/l) In conclusion : we can agree with the proposed environmental classification by the UK competent authority. Editorial comment: On table 21, the DT50 of the aerobic water sediment test is stated as 61.9-776.2 days, we believe that it should read 61.9-76.2 as stated further in the text.				
Dossier Submitter's Response				
Thank you for your comment. We agree that table 21 should read 61.9-76.2 days as noted.				
RAC's response				
Noted				

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2016	Germany		MemberState	22

Comment received

We support to use the static study with Lemna gibba (Hoberg, 1992e) and the static study with Pseudokirchneriella subcapitata (Hoberg, 1992a and reassessment by Dorgerloh, 2004b) as key studies for the classification and labeling of Asulam sodium. However, we would prefer to use the ErC50 (9d) = 0.186 mg/L / ErC50 (6d) = 0.205 mg/L from the Lemna study for acute aquatic hazard classification instead of the ErC50 (14d) = 0.16 mg/L, all based on mean measured concentration.

Additionally, we would prefer to use the NOErC (14d) = 0.051 mg/L mean measured derived from the Lemna study and the NOErC (72h) = 0.02 mg/L mean measured derived from the static study with Pseudokirchneriella subcapitata (Hoberg, 1992a and reassessment by Dorgerloh, 2004b) for chronic aquatic hazard classification instead of the NOErC (14d) = 0.011 mg/L nominal for Myriophyllum spicatum (Seeland, 2014), because in this study the test substance was a 400 g/L soluble liquid formulation and not a pure active ingredient like in the key studies or other relevant studies.

These minor recommends have no influence on the classification and labeling for environmental hazards of asulam sodium as stated above.

Dossier Submitter's Response

We understand that it may be preferable to use a ≈7-day endpoint from Lemna studies instead of those at 14-days - particularly where the test substance is not stable throughout the test or there are indications of a reduction in growth by day 14 due to nutrient depletion. In the Lemna study by Hoberg (1992e) concentrations of pure asulam decreased to 15% of nominals at test termination, however endpoints at 14 days were based on mean measured concentrations. It was also reported that 'there was good growth throughout the 14-days in controls (meeting validity criteria) indicating no problems with nutrient depletion'. In this case we feel the Lemna 14-day ErC50 endpoint may be suitable to use for classification (it was also used for risk assessment) - but, as noted, it makes no difference to the classification proposal whether endpoints at 6, 9 or 14 days are chosen. The NOErC is also the same at 6, 9 and 14-days (at 0.051 mg asulam sodium/L). The eventual choice of ErC50 could be left to the RAC.

As the formulation study on Myriophyllum (Seeland, 2014) used a simple solution of asulam in water, with no other coformulants or solvents to confound the toxicity, it was felt that an endpoint based on the asulam sodium equivalent concentration would be suitable to use for classification. If the RAC does not consider it appropriate to use the Myriophyllum NOErC - then, as noted, the NOErCs from the Lemna or P. subcapitata studies are also suitable and would not change the chronic classification proposal.

RAC's response

Noted