Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

SULCOTRIONE

ECHA/RAC/ CLH-O-0000002100-96-01/A1

Adopted

27 October 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: Sulcotrione
CAS number: 99105-77-8
EC number:

General comments

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comments
01/03/2011	France / MSCA	We disagree with the proposed toxicological classification and suggest instead (please see detailed comments below): Directive 67/548/EEC: Xn, Carc. cat 3 R40, R43 GHS criteria : Carc. 2 H351 Skin sens. 1 H317	See below.	RAC does not agree with the FR CA that classification for carcinogenicity is required (see below).
02/03/2011	UK / MSCA	P4. In the "proposed labelling" section, please check the safety phrases – we would suggest that S24-37 should also be used.	We agree with the proposal of UK. Unfortunately these phrases have been forgotten in our CLH-Report.	Given the final RAC position regarding classification for reproductive toxicity, S36/37 was considered to be more appropriate than S24-37.
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.	We agree with the proposal of Sweden which is the correct form for reference.	The RAC opinion has been prepared according to the agreed format; with reference to the relevant EU legislation.
03/03/2011	Portugal / Maria do Carmo Palma / Portuegese Environment Agency	Considering the present proposal, we agree to establish a harmonised classification & labelling for Sulcotrione. The proposed environmental classification and labelling fulfills the criteria established both in CLP Regulation and 67/548/EEC Directive. Therefore, we support this proposal.	Thank you for the support.	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	Thank you. As far as labelling is concerned, we agree and only H410 is proposed. However, if	Noted Noted

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		redundant, therefore the H410 alone should be applied.	a substance is classified for both acute and chronic aquatic toxicity, both Hazard statements are assigned (compare Article 27 of EC 1272/2008 and Tab. 4.1.6 CLP-Guidance). Hence, we maintain H400 and H410 for the classification section.	
		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.	We agree and a clarification is added (p. 5).	Noted
03/03/2011	Spain / Elina Valcarce / MSCA	Spain supports the German proposal.		Noted

Carcinogenicity

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comments

01/03/2011	France /MSCA	5.7 Carcinogenicity: We agree that the highest dose tested in the mice study exceeded the tolerated dose (survival is below 50% for females). However, considering the fact that the 3000 ppm survival is quite similar to other doses and the body weight is not affected, this dose does not seem to be over the MTD. Thus, the adenocarcinomas observed in females at 3000 ppm should be considered as relevant since the genotoxicity potential is not completely excluded. In our point of view, a classification Xn, Carc. cat 3 R40 (cat 2 for carcinogenic substances, H351) should be appropriate.	Mortality of female mice at 3000 ppm is initially very similar to the curve at 7000 ppm. We do not consider the few adenocarcinomas at these high doses sufficient evidence for a carcinogenic potential.	RAC agrees with the Dossier Submitter; further information on mammary adenocarcinoma in female mice was found in the DAR. Survival of female mice in the 3000 ppm group was similar to that of the 7000 ppm group at 65 weeks but at termination of the study was similar to the controls. RAC judged the MTD to have been exceeded at 3000 ppm. A discussion of this and other aspects considered in reaching a final position has been added to the BD/Opinion.
02/03/2011	UK /MSCA	P31. We agree that the available data for carcinogenicity (oral) do not support classification for this endpoint.	Thank you	Noted

Mutagenicity

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comments
02/03/2011	UK / MSCA	P26. In vitro data. Whilst the study by Howard (1989) in Table 16 gives a negative result, the top dose tested was much lower than the top dose tested in the other studies and so does not provide support to the overall conclusion that sulcotrione is not genotoxic. P28. Summary and discussion. We would suggest placing less relevance on the negative result obtained from the UDS assay. It is our understanding that this test has a high incidence of false negatives and is a poor follow-up to a negative in a micronucleus test (see Kirkland, D. and Speit, G. (2008) Evaluation of the ability of a battery of three in vitro genotoxicity tests to discriminate rodent carcinogens and non-carcinogens III. Appropriate follow-up testing in vivo. Mutation Research 654:114-132). However, considering the majority of negative results in the in vivo micronucleus assays (weak positive in only one assay at doses that exceeded the limit dose), the absence of carcinogenic effects and the lack of evidence for germ cell effects, we agree with no classification.	Sulcotrione was not genotoxic in human lymphocytes up to a concentration that reduced the mitotic index by about 50 %. This does support the overall conclusion. In our understanding none of the currently used mutagenicity assays reliably predict the carcinogenic potential of a test substance. The UDS assay tests one possible mechanism for carcinogenicity that is not covered by any of the other tests. It can produce false negatives for DNA damage if the DNA segments replaced by the damage response are not large enough to be detected. Clearly the presence or absence of an carcinogenic effect in	RAC agrees with the Dossier Submitter. RAC agrees with the Dossier Submitter. The negative result is not a “false” negative.

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			the long-term studies has a higher relevance for the detection of rodent carcinogens.	

Toxicity to reproduction

/Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comments
01/03/2011	France / MSCA	5.8 Toxicity for reproduction: As offspring urinary tract effects occurred at parental toxic dose (M) and these effects were not observed in the teratogenicity studies, we agree that the classification Xn, Repr. Cat 3 R63 is not appropriate.	Thank you	Agreed, but the evidence of increased mortality in young pups does justify classification for developmental effects.

2/03/2011	Sweden / Ing-Marie Olsson / MSCA	The reproductive studies in rats reveal a nephrotoxic effect in all generations that shows a tendency to increase with the generations. This effect is, however, not considered in any of the proposed classifications. According to our understanding it should be considered whether the effects observed justify STOT RE Category 2 (H373) for nephrotoxicity, based on the LOAEL 14 mg/kg bw/d in the 2-generation study or a classification for Reproductive toxicity Category 2 (H361) according to Reg. (EC) No 1272/2008 and Repro Cat 3 (R63) according to Directive 67/548/EEC. We agree with the conclusion on the EFSA peer-review of sulcotrione (EFSA Scientific report 2008:150) that "Reproduction toxicity studies reflect the same effects in parents, but abnormalities of the urinary tract were increased in pups of both generations, not observed in the first parental animals". This can be seen in the DAR for Sulcotrione (Annex B-6) that presents an • increased effects on the kidney after in utero exposure (i.e. P0 compared to P1,Table B.6.6-7 and Table 6.6-9, page 55-56), • increased number of urinary tract malformations in the F2 pups compared to the F1 (Table B.6.6-13, page 58) • presence of misshaped and reduced kidneys judged to be treatment related observed in both of the 2-generation studies (page 58 and Table B6.6-23, page 65). These data could indicate that exposure in utero makes the kidneys of the growing individual more sensitive to sulcotrione exposure which would warrant a classification for reproductive toxicity. Additional arguments for reprotox classification can be found in the CLP classification criteria – according to section 3.7.1.4. "Developmental toxicity includes, in its widest sense, any effect which interferes with normal development of the conceptus, either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or postnatally, to the time of sexual maturation." We consider that the body of evidence meets the criteria for the classification for reproductive toxicity.	It is unclear whether the effect on offspring kidney development represents a direct toxicity of sulcotrione. Milk excretion data are not available.It should be kept in mind that tyrosine content of the milk may be much higher than normal for exposed groups due to high plasma concentration in dams. This is relevant for rats but would not be relevant for humans who use different pathways of coping with the consequences of HPPD inhibition and do not develop hypertyrosinemia	In summary, the renal effects were consistent with the direct toxicity observed in repeated dose studies (for which a STOT classification is considered appropriate). In these studies, the effects occurred in adults that had not been exposed *in utero*. Further, the effects were not seen in pups examined at term in standard developmental toxicity studies. However, RAC still concluded that the developmental toxicity as evidenced by increased pup mortality justified classification.

02/03/2011	UK / MSCA	We feel that section 5.8.5 (p32) would benefit from some additional information, such as the dose levels at which effects were observed, the number of animals affected and further details about the kidney malformations/urinary tract abnormalities, and at which time points they were detected. This would help in the interpretation of the data. P32. Please consider putting doses in mg/kg bw/day in the dose column of Table 19 to assist the reader in analysing the data. P33. Summary and discussion. The effects on pups' kidneys are consistent with the findings in repeated dose toxicity studies, indicative of sulcotrione causing direct toxicity rather than a specific developmental effect; the absence of kidney effects and malformations during developmental studies support this conclusion. However, since these effects develop during lactation, it is possible that direct toxicity occurs via lactation. This possibility should be discussed in the context of possible dietary intake by the pups and/or coprophagia and classification for effects on or via lactation. We note from the evaluation report produced under the Directive 91/414/EEC review that these effects were evident at lactation day 4, which would support classification for R64/H362. P33. We agree with the decision not to classify for fertility	Sulcotrione has been reviewed in the programme covered by Commission Regulation (EC) No 1490/2002. Detailed information on these studies can be found in the Draft Assessment Report. Regarding kidney toxicity in offspring see response to Sweden.	The Rapporteurs consulted the DAR themselves and included the additional information required to enable a full and transparent evaluation. Perhaps this task could have been done more efficiently by the Dossier Submitter themselves. The Rapporteur included a discussion of the possibility of effects occurring on or via lactation in the BD and the Opinion. RAC concluded that no classification for effects on or via lactation (H362) would be appropriate.

03/03/2011	Austria / Austrian Agency for Health and Food Safety	Xn, R63 / Repro Cat 2, H361d - In the CLH report it is stated that the R63 was proposed in the EFSA Scientific report (2008) based on urinary tract abnormalities observed in rat offspring at weaning and as adults in the rat multigeneration studies - However, the argumentation of MSCA that Xn, R63 / Repro Cat 2, H361d is not appropriate, can be followed for following reasons: - Kidney is, among others, the target organ of sulcotrione and the effects on kidneys (weight and histopathological findings) were observed in several studies - Renal pelvis dilation was not apparent at birth but became a frequent finding in high dose pups up to adult age - Effects on urinary tract were not observed in the developmental toxicity studies even though the highest dose administered to the rat dams was 3 times the dose achieved in the two-generation study - small or misshaped kidneys were found in a few high dose offspring in the two-generation studies after the lactation period but not in the developmental toxicity study where evaluation of foetuses is performed at term of pregnancy Conclusion: Based on the overall picture of sulcotrione and on the fact, that the effects on urinary tract are shown to arise during the life and not to be caused in utero (no findings in developmental studies with much higher dose), classification and labelling as Xn, R63 / Repro Cat 2, H361d is not fully supported.	Regarding kidney toxicity in offspring see response to Sweden	RAC agrees that these observations do not justify classification for developmental toxicity. However, see also the responses to comments from the SW CA and UK CA.
03/03/2011	Spain / Elina Valcarce / MSCA	p. 33 Summary and discussion on reproductive toxicity Spain agrees with Germany that a classification for reproductive toxicity is not warranted. In the two-generation studies in rats, in the offspring, variations of the urinary tract (dilated ureter and/or renal pelvis) were observed. Misshapen and smaller kidneys (both in a very low incidence) were also seen. All these findings were observed in the presence of parental toxicity, such as corneal opacity and keratitis, increase in kidney and liver weights, renal pelvis dilation and/or nephropathy. In the development studies in rats an increase of the number of foetuses with extra ribs (not statistically significant) was observed. The incidence of incompletely ossified sternum was increased at the highest dose without reaching statistical relevance and within historical control data incidence. In rabbits, an increase of full-sized extra ribs was observed, but among the historical control data. Despite EFSA proposal for R63 (Possible risk of harm to the unborn child), Spain considers that all these effects are not sufficiently severe to justify a classification for developmental toxicity	Thank you	RAC noted these arguments against classification for developmental toxicity. Also see above.

Respiratory sensitisation

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comments
		No comments received.		

Other hazards and endpoints

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comments
01/03/2011	France / MSCA	Identity P 7, point 1.2: composition of the substance: The minimum purity should be mentioned as ≥ 950 g/kg and not > 950 g/kg. Other human health hazards P21, Eye irritation: Agree. The irritation observed is moderate and the score do not match the trigger values for classification. Physical hazards Page 32 - 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 8 point VII, 7.10; Page 32 - paragraph 6, point 6.2 – flammability : Could you please give some details to be able to classify sulcotrione as not flammable and not only not highly flammable. Environmental hazards P38, table 25 and P40, table 26: There is a discrepancy on the EAUCC50 value of sulcotrione on Lemna gibba indicated in both tables. Indeed, this toxicity value is indicated to be 0.0062 mg/L in table 25 and 0.062 mg/L in table 26. Could you please check?	Correct. All relevant information can be found in the draft assessment report. We checked and corrected accordingly.	The BD reflects this. RAC does not consider these additional details to be necessary given the absence of any concern about these endpoints on previous evaluation.
02/03/2011	Sweden / Ing-Marie Olsson / MSCA	Skin sensitization: SE supports classification of sulcotrione (Cas No 99105-77-8) as a skin sensitizer 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 sensitizers into subcategories 1A and 1B will be introduced. We suggest that this is	Classification proposal followed the then current version of Regulation (EC) No 1272/2008.	RAC supports the classification of sulcotrione as Skin Sens 1A; H317. The rationale for doing so has been

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		considered in the report. Thus, for sulcotrione it would mean that it is a category 1A sensitizer as the intradermal induction dose was ≤ 1% in the study referred to.	However, adaptation to the future version is considered possible as concentration for intradermal induction and challenge is given in the report.	added to the BD.
		Environment: In general we agree with the proposed classification of sulcotrione and the M factor; however we have the following comments: Biodegradation We agree that the substance is not ready biodegradable; however we have reached this conclusion based on a slightly different rationale. No ready test for the substance is available. The hydrolysis study showed that the substance was abiotically stable. However, the available water/sediment study determined DT50 in water phase between 9 and 15 days. In addition formation of a metabolite CMBA was measured (which can give reason to believe that this formation is biologically mediated since this was not measured in the hydrolysis study). Thus, in our opinion since the DT50 was below 16 days a criterion for a fast primary degradation was met (see decision logic for assessment of biodegradation, section II.4 of the guidance document on application of the CLP criteria). In order to assess whether the substance is or is not ready biodegradable as assessment of the formed metabolite(s) should be performed. If the formed metabolite(s) are classifiable the parent compound should be regarded as not ready biodegradable. However if the metabolite(s) are not classifiable the parent compound should be regarded as ready biodegradable. Based on the toxicity data of the metabolite CMBA it can be concluded that this metabolite meets the criteria for Aquatic Chronic 3 classification (R52-53) and therefore sulcotrione can be regarded as not readily biodegradable.	We agree that this is another rationale. As this does not change the outcome, we did not change the CLH-report.	It might have been helpful if the Dossier Submitter had considered these arguments n the original CLH report. However, RA does not believe that rapid primary degradation was occurring, so agrees that the outcome is not affected.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON SULCOTRIONE

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comments
		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: The log Pow of sulcotrione and of its major metabolite CMBA has been determined as ≤ 0.2 (pH 4-9), therefore a bioconcentration in aquatic organisms is unlikely. Sulcotrione does not fulfil the trigger of log Pow ≥ 3 (criterion for bioaccumulating potential conform Directive 67/548/EEC) and log Pow ≥ 4 (criterion for bioaccumulating potential conform Regulation EC 1272/2008). This comment applies also to section 7.6 on conclusion on the environmental classification and labeling. We propose also to delete "and its major metabolite MCBA" since this information has no consequence on the assessment of the bioaccumulation potential of sulcotrione.	References to metabolite deleted. Done accordingly.	The MSCA comment appears to contain an error – presumably they agree that the substance does NOT meet the criteria for bioaccumulation. Other comments noted.
02/03/2011	UK / MSCA	P20. We agree that the available data for acute toxicity (oral, dermal and inhalation) do not support classification for these endpoints. However, please check the summary and discussion of acute toxicity – it states that the dermal route was in rats (should this be rabbits?) and the inhalation route in rabbits (should this be rats?). Also, it is not clear where the statement 'LC50 > 5.06 mg/L' comes from – this value is not stated in Table 8. P21. We agree that the available data for skin irritation do not support classification for this end-point. P22. From the information given for eye irritation, it is likely we would agree that classification is not required for this end-point. However, it is not completely clear from Table 11 and the summary/ discussion in section 5.2.5 that the classification criteria are not met. For example, for a 6 rabbit test the classification criteria for CLP are based on mean scores in 4 out of 6 rabbits – it is not possible to deduce from the information provided that these criteria are not met. Please consider expanding/revising this section to clarify. P23. We agree that the available data for skin sensitisation support classification as Xi; R43 / Skin Sens. 1; H317. However please consider expanding section 5.4.3 to explain what the classification is based on	Has been corrected. Detailed information on these studies can be found in the Draft Assessment Report (DAR) prepared under Commission Regulation (EC) No 1490/2002. See DAR	Noted Noted Noted RAC supports the classification of sulcotrione as Skin Sens

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON SULCOTRIONE

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		(i.e., a positive response in ⍰ 30% of animals in an adjuvant assay). P24. Please give some indication in section 5.5.1 (or in table 13, p23) of the magnitude of the sizes of the increases in liver and kidney weights so that the reader can decide if these effects are adverse. P24-25. We agree that the available data for repeated dose toxicity (oral, dermal) presented in this section do not support classification for this end-point. However, owing to the severity of the effect, we would welcome further information and discussion in section 5.5.4 and/or 5.5.5 to explain why the corneal effects are not considered to be relevant to humans (e.g., include information on the TAT pathway, which can help to explain species and sex differences). Also, in section 5.5.4 it would be helpful to explain what NTBC is, e.g. nitisinone (related to sulcotrione) used in therapy for tyrosinaemia Also, please consider including a discussion about the data derived from the carcinogenicity testing (p30, Table 18) and its relevance to repeated dose classification. For example, in the study by Potrepka and Turnier (1991), kidney effects in male rats occurred from 0.04 mg/kg/d.	See DAR Sulcotrione and tyrosine both are believed to have caused the kidney effects in male rats in the repeat dose studies. The relative contribution of each compound is difficult to estimate. However, while renal excretion of sulcotrione is comparable between sexes, kidneys of female rats were not similarly affected. This might argue for a higher contribution of tyrosine in the males.	1A; H317. The rationale for doing so has been added to the BD. The Rapporteur consulted the DAR for further details. These data from the carcinogenicity studies were of relevance to repeated dose classification. RAC agreed that classification for repeated dose toxicity could be supported by these renal findings.
03/03/2011	Spain / Elina Valcarce / MSCA	p. 23 Summary and discussion on sensitisation The Spanish CA supports the proposed classification of sulcotrione 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 study of Magnusson & Kligman results after challenge and delayed contact hypersensibility induced in 16/20 guinea pigs (30% challenge application) and in 14/20 animals (10% challenge application).	Thank you	RAC supports the classification of sulcotrione as Skin Sens 1A; H317. The rationale for doing so has been added to the BD