Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Tralkoxydim

EC number: -

CAS number: 87820-88-0

ECHA/RAC/CLH-O-0000001911-78-03/A2

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Adopted

15 September 2012

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: Tralkoxydim
EC number:
CAS number: 87820-88-0

General comments

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
12/09 /2011	Spain / MSCA	We are in agreement with the classification proposal submitted by UK.	Thank you for your comment.	The support is noted.
07/10 /2011	Switzerland / Syngenta Crop Protection AG	Please find the attached position statement to the comments made in the CLH Report dated August 2011 *ECHA comment: The document (Tralkoxydim - Proposed Public Comments FINAL (07.10.2011).docx) "**Tralkoxydim** Comments on the EChA Annex VI Report (Proposal for Harmonised Classification & Labelling) submitted by the United Kingdom August 2011" is copied below:* **Tralkoxydim** **Comments on the EChA Annex VI Report (Proposal for Harmonised Classification & Labelling) submitted by the United Kingdom August 2011** **October 2011** **<u>Astrocytomas (R40)</u>**	Thank you for your comments. An increase in the	RAC considered the small increase in (rare)

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		It is Syngenta's position that the brain and spinal cord astrocytomas in males in the 2 year feeding study in rats are unrelated to treatment because: • The incidence of each tumour type in the top dose males is not significantly increased compared to concurrent controls (brain: 2/52 in control males versus 3/52 in top dose males; spinal cord: 0/52 in control males versus 1/52 in top dose males) and there was no increased incidence in females at any dose level. • Although slightly above the concurrent controls, the incidence of brain astrocytomas in top dose males (3/52) is within the contemporaneous historical control incidence (up to 3/52) for the conducting laboratory in studies initiated both before (and running concurrently with) and after the study conducted with tralkoxydim (initiated 1985, terminated 1987). • The incidence of spinal cord astrocytomas in top dose males (1/52) is consistent with the control incidence in male Alpk:ApfSD rats (up to 1/52). • Known and suspected/equivocal neurocarcinogens in rats tend to be mutagenic in bacterial assays in the presence of metabolic activation; tralkoxydim is not genotoxic *in vitro* or *in vivo.* • Despite the fact that hamsters are susceptible to neurocarcinogens, no brain or spinal cord tumours were noted in the 80 week hamster study with tralkoxydim, supporting the position that tralkoxydim is not a neurocarcinogen. **<u>Developmental Toxicity in the Rat (R63)</u>** Syngenta agrees that no classification is required for developmental toxicity. Regarding the single instances of misshapen sacral vertebrae at	incidence of brain and spinal cord astrocytoma was noted. Due to the rare nature of such tumours, the observed incidence was considered to be treatment related. However we agree that the increase was observed at the top dose, in male rats only and the incidence was at the upper level observed in contemporary historical controls. We note the information	brain and spinal cord astrocytomas observed in male rats at the highest dose only not related to treatment. The increase was not statistically significant and incidences were still within the historical control range. Further, no such increase was observed in female rats or hamsters. The support and information provided is noted.

<table>
<tr><th>Date</th><th>Country / Organisation / MSCA</th><th>Comment</th><th>Dossier submitter's response to comment</th><th>RAC's response to comment</th></tr>
<tr><td></td><td></td><td>30 and 3 mg/kg/day in the first and second studies, respectively, it is Syngenta's position that these findings are within historical control data and that historical control data generated after 1988 should be considered more relevant for this particular finding.

Both study reports were revised after initial issue following a reassessment of foetal skeletons. As explained on page 6 of both reports:

"At first reading any foetuses with a direct connection between adjacent vertebrae were recorded as having a defect, slightly misshapen vertebrae were ignored. Following additional experience with defects of this type it was considered that these misshapen vertebrae formed part of a continuum of change and the skeletons were reassessed."

As a consequence of this reassessment misshapen centra were logged as a single effect whereas prior to this they would most likely either have not been recorded or possibly recorded as a minor/variant change in ossification.

Based on the above, it is clear that any study reported prior to the re-read of the studies on tralkoxydim would not have consistently included any recorded instances of misshapen centra as a separate defect. Thus data reported before the re-read (i.e. before 1988) would be less relevant in terms of providing the historical control incidence of this defect.

When both of the tralkoxydim studies were re-read no effects of vertebral centra were noted in the control groups and an association with treatment at 3 and 30 mg/kg could not be discounted. However, since that time the defects have been seen in control animals:

<table>
<tr><th rowspan="2">Study date</th><th rowspan="2">No. foetuses</th><th colspan="3">No. of findings</th></tr>
<tr><td>Vertebral</td><td>Misshapen</td><td>Either</td></tr>
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</td><td>provided.</td><td></td></tr>
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		fusions (1)	vertebrae (2)	(1) or (2)
April 1986	218	0	2	2
April 1987	803	0	0	0
Sept 1987	282	0	0	0
Sept 1987	302	0	0	0
Nov 1987	276	0	0	0
Jan 1988	281	0	0	0
Feb 1988	297	0	0	0
May 1988	277	0	0	0
Jun 1988	117	1	1	2
July 1988	1877[a]	0	2	2
Nov 1988	241	0	0	0
April 1989	265	0	0	0
July 1989	272	0	0	0
Sept 1989	307	0	2	2
June 1990	259	0	0	0

Key: a: One investigative study (confirmed by company).
In-life phases for the study with tralkoxydim: 20 August 1985 to 28 September 1987.

This supports the view that, although occurring before 1988, such defects have been recorded consistently as 'misshapen vertebral centra' only since 1988.

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		Based on studies read since 1988, an incidence of 1 or 2 animals per group showing such a defect can be concluded as consistent with the sporadic incidence in control animals. Thus the incidence of 1 animal (2 vertebrae affected) at both 3 and 30 mg/kg in the tralkoxydim studies falls within the background incidence. **<u>Liver Toxicity (STOT-RE 2/R48)</u>** Classification with STOT-RE2/R48 has been proposed based on effects in the liver in the 90 day and 1 year dog studies. It is Syngenta's position that the liver changes observed in these studies are not of sufficient adversity to warrant classification with STOT-RE 2/R48. These liver effects do not appear to have any impact upon the well being of the animal and do not increase notably in magnitude when the duration of dosing is increased from 90 days to 1 year. In addition, the incidence of fatty change in the liver of male dogs at 5 mg/kg/day (moderate in 1/4 males) is of no toxicological relevance as it is not accompanied by any correlating changes in clinical chemistry, haematology or macroscopic findings and is accompanied by only a marginal increase in liver weight of <10%. Furthermore, these liver findings are confined to the dog and are not seen in the rat or hamster and those liver effects identified in the mouse are shown to be species-specific and therefore not relevant for human health hazard or risk assessment.	We consider that significant effects (fatty changes in hepatocytes) were observed in the dog. These effects were observed in the 90 days study and also in the 1 year study at low doses that are considered relevant for classification.	When looking solely at the liver effects in dogs following tralkoxydim treatment, RAC considered the fatty change in itself not to meet the criteria for classification for repeated dose toxicity. When looking at the liver effects in combination with the observed changes in clinical chemistry, haematology and effects on the adrenals, there seems to be a dysfunction of the liver with possible secondary effects on other organs like the adrenals. Classification for these combined effects is, however, a borderline case. Therefore, two options are presented (one for no classification, one for STOT RE2) that need to be further

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		<u>Self-Classification</u> Syngenta does not propose self-classification with Carc Cat3; R40 as described in section 2.4.2. Version **Final**: 07 October 2011. *End of attachment*	We acknowledge these comments. The self classification was included in error.	discussed. Noted.
12/10 /2011	Germany / MSCA	The German CA supports the proposed classification of Tralkoxydim. We propose to include the chemical name '2-[1-(ethoxyimino)propyl]-3-hydroxy-5-(2,4,6-trimethylphenyl)-2-cyclohexen-1-one' along with the ISO name 'tralkoxydime' in the Annex VI entry.	Thank you for your comment.	The support is noted.
14/10 /2011	Finland / Finnish Safety and Chemicals Agency / MSCA	The CLH report is very clear and well written.	Thank you for your comment.	Noted.
14/10 /2011	Denmark / MSCA	The substance have been evaluated by EFSA under peer review programe. Denmark have earlier agreed with their conclusion. The end-point list is attached.	Thank you for your comments. We have addressed you additional comments below.	Noted.
14/10 /2011	France / MSCA	We have some precision to be asked on the carcinogenicity and we do not agree with the not classification of the toxicity on reproduction.	Thank you for you comment. We have addressed your individual comments below.	See response to specific endpoints below.

Carcinogenicity

Date	Country / Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
07/10/2011	Switzerland /	See General comments.		

Date	Country / Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
	Syngenta Crop Protection AG			
12/10/2011	Germany / MSCA	DE supports the proposed classification for tralkoxydim: Carc Cat 3; R40 and Carc. 2 – H351, respectively	Thank you for your comments.	The support is noted.
14/10/2011	Finland / Finnish Safety and Chemicals Agency / MSCA	We find the proposed classification Carc. 2 justified.	Thank you for your comments	The support is noted.
14/10/2011	Denmark/ MSCA	Agreed.	Thank you for your comments	The support is noted.
14/10/2011	France / MSCA	Taking into account the tumours incidence and the dose level at which they occurred, a carcinogenic classification Cat 1B should be excessive, therefore we agree with the Cat 2 proposed by the RMS. However, since 2 kinds of tumours were found on 2 different species, we would like to have some precisions on these tumours. - Could you precise if the Leydig cells tumours observed on rats are benign or malignant? - In the Hamster study, please precise if the "sex cord stromal tumours" include testicular effects or are restricted to ovaries.	Thank you for your comments. We can confirm that the leydig cell tumours were benign. No neoplastic effects were observed in the testes in the hamster study. However the non-neoplastic effects were observed and these are reported in the dossier.	The support is noted, as is the extra information provided by MSCA.

Mutagenicity

Date	Country Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment

Toxicity to reproduction

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
07/10 /2011	Switzerland / Syngenta Crop Protection AG	See General comments.		
12/10	Austria /	In the EFSA Scientific report (March 2008) a classification for	Thank you for your	

/2011	Austrian Agency for Health and Food Safety	Tralkoxydim with Xn ,Repr. Cat. 3, R62 and Xn; Repr. Cat. 3 R63 is proposed while in the CLH report the data are considered to be "conclusive but not sufficient for classification." - Xn; Repr. Cat. 3 R62 / Repro. Cat 2, H361f: According to the EFSA Scientific report (March 2008) classification with R62 is based on the following adverse effects on gonads in hamsters, rats and dogs in subchronic and chronic studies: - Hamsters: testis weight increased (absolute 6% and relative 11%) at 12000 ppm (700.3 mg/kg/day); slight increase in testicular tubular degeneration - Rats: enlarged testis, increase of white aereas in testis (at 500 and 2500ppm) - Dogs: decreased epididymides weight (21%) was noted along with slight unilateral atrophy of the seminiferous epithelium in 1 male of the 50 mg/kg/day group, unilateral tubular degeneration was observed in 1/4 males at 0.5 and 50 mg/kg/day. Bilateral tubular degeneration was noted in 1/4 males at 0.5 mg/kg/day and 5 mg/kg/day) in subchronic and chronic studies. No further studies on mechanistic background of these findings have been provided in order to demonstrate species specifity. Therefore relevance of these findings to human cannot be excluded. There were no treatment related effects on reproductive parameters reported in the rat multigeneration study (dose groups: 0, 50, 200 or 1000ppm), but the findings on gonads in three different species should be discussed by ECHA experts. Classification with Repro. Cat 2, H361f or STOT RE 2 H373 should be considered.	comments. We acknowledge that effects were observed in the gonads of rats, dogs and hamsters in the short-term and chronic studies. We have included all available and relevant information in the proposal and have no further comments that would provide additional clarification at this stage. We therefore welcome discussion of these issues by RAC.	RAC concluded that the effects observed on the male gonads in subchronic and chronic studies with rats, hamsters and dogs provide insufficient evidence for an effect of tralkoxydim on sexual function and fertility, and thus supported the proposal for non-classification for fertility. - The increase in testis weight in hamsters was only small, as was the increase in testicular tubular degeneration. The latter increase was not statistically significant, and also the severity of the degeneration did not clearly increase with dose. – In rats, the increase in large testes with white areas was without accompanying effect on testicular weight. Other effects in rats

		- Xn; Repr. Cat. 3 R63/ Repro. Cat 2, H361d: The classification with Xn; Repr. Cat. 3 R63 is proposed by the RMS in the DAR (2005) and the PRAPeR experts agreed to propose this classification for Tralkoxydim based on the following findings: - The classification is based on observations of misshapen/fused vertebrae in the two rat developmental studies. These effects were seen at top dose levels (300mg/kg BW/d/ and 200 mg/kg BW/d, respectively) in both studies in the presence of severe maternal toxicity. In both studies there were also single incidences in the mid dose groups (30 mg/kg BW/d and 3 mg/kg BW/d, respectively) in absence of maternal toxicity. Such findings are completely absent in controls and historical control data show that misshapen or fused vertebrae are very rare events. Therefore these findings – although occuring at high dose level - should not be disregarded. - In the rabbit severe maternal toxicity, reduced body weight and food consumption during dosing, a high rate of abortions, reduced implantations, live foetuses, foetuses per litter and a statistically significant increase in late intra-uterine deaths were observed. There was a significant enhancement of pre-implantation losses observed in all dose groups (13,0; 10,3 and 20;9% of the 2,5; 20 and 100mg/kg BW/d group) compared to 3,6% in control animals. In the CLH dossier the findings are regarded to be not sufficient for classification. However, classification for Tralkoxydim with Repro. Cat 2, H361d should be considered by ECHA experts.	The effects observed at 200 and 300 mg/kg/day occurred in the presence of marked maternal toxicity. A single incidence was observed at 30 and 3 mg/kg in the 2 respective studies. We agree that these findings are rare, as stated in the report. We have included all available and relevant information in the proposal and have no further comments that would provide additional clarification a this stage. We therefore welcome discussion of these issues by RAC.	were, at least partially, secondary to Leydig cell hyperplasia and/or tumours, and were age-related. - Effects in dogs were minimal, occurred without accompaying weight (testis) or microscopic (epididymes) changes, were related to general toxicity or occurred without apparent dose-response relationship. RAC concluded that the effects observed in rats and rabbits do not warrant classification for developmental toxicity, and thus supported the proposal for non-classification for this endpoint. - In line with the criteria, effects observed in rats at dose levels that resulted in excessive maternal toxicity (200 and 300 mg/kg bw/day) have not

				been considered for classification purposes. Effects in rats at non-maternally toxic levels are within the historical control range or are only indicative for delayed development. - Also for rabbits, effects observed at the dose level that resulted in excessive maternal toxicity (100 mg/kg bw/day) have not been considered for classification purposes. Effects at lower dose levels were not dose-related and still within the historical control range.
14/10 /2011	Finland / Finnish Safety and Chemicals Agency / MSCA	In our opinion, the justification for no classification for developmental toxicity is not conclusive. We think that this is a borderline case.	Thank you for you comments. We agree that this is a borderline case. We have included all available and relevant information in the proposal and have no further comments that would provide additional clarification at this stage. We therefore welcome discussion of these issues by RAC.	See response above to the Austrian comments.

14/10 /2011	Denmark / MSCA	I do find that there is evidence of damage to the reproduction. Tralkoxydim possess properties expected to be a risk to reproduction in animals probably caused by endocrine disrupting properties of the substance. Effects assessed to be harmful for reproduction are seen in three animal species despite the facts that no such effects are seen in the actual reproduction study. However effects related to reproduction in the other studies were seen after prolonged exposure, which could be the reason why these effects do no turn up in the reproduction study with a shorter duration. It is also well-known that the sperm numbers in rats can be substantially reduced before fertility is affected. Both in rats and hamsters considerable effects are seen on sex organs in terms of testicular tubular atrophy, reduced numbers of spermatozoa in the epididymides accompanied by the presence of an increased number of early nucleated sperm precursor cells in rats and an increase in testosterone hydroxylation in male hamsters. Furthermore increased incidence of benign ovarian tumours in female rats were observed (possibly linked to the endocrine disruption); LOAEL respectivly 162,8 mg/kg bw/day and 700 mg/kg bw/day. In the dog studies (90 days and 1 year study) the doses used was generally low with a maximal tested dose of 50 mg/kg bw/day and the preliminary study indicates that testicular atrophy first occurs at doses higher than 50 mg/kg bw/day. In the preliminary study with 1 dog the highest dose 170 mg/kg bw/day elicit the same effects as in the two other species; degeneration of the testicular tubular cells, absence of sperms in the epididymides and adrenal effects (vacuolation; testosterone synthesis also takes place in the adrenals). In the 1 year dogs study increased vacuolation in adrenals were also seen from 50 mg/kg bw/day in males and from 5 mg/kg bw/day in females. Based on these facts the Danish EPA has concluded that the substance should be classified R62 Risk of impaired fertility. The structural related molecule tepraloxydim has a similar toxicological profile and has also been classified R40, R63 and R62 by ISPRA/ECB (September 2004) The R62 classification are based on the same critical effects as seen for tralkoxydim however the effects were more pronounced expressed for	Thank you for your detailed comments. We have included all available and relevant information in the proposal and have no further comments that would provide additional clarification at this stage. We therefore welcome discussion of these issues by RAC. We note the classification of the related molecule tepraloxydim. However, we note that there are also differences in the	See response above to the Austrian comments. Given the differences in toxicological profile between tralkoxydim and tepraloxydim, the suggested comparison is not

		tepraloxydim.	toxicological profiles of these two substances. For example, the effects in dogs included testicular degeneration, loss of spermatids, azoospermia etc. Also, the developmental effects observed with tepraloxydim are different to those observed with tralkoxydim, and included specific heart malformations.	considered appropriate.
14/10 /2011	France / MSCA	We wonder if malformations such as cleft palate or anasarca can be induced only by maternal toxicity. More details on these malformations as individual data on pups and dams could be interesting. Moreover, in both rats developmental studies, variations (such as misshapen vertebrae) are observed in pups, without toxic effect on dam (at 3 and 30 mg/kg/d). At high dose level, these variations are still observed besides the malformations. Considering these effects, classification in category 2 for possible developmental effect (Repr. 2 H361d) is proposed. A category 2 classification for fertility (Repr. 2 H361f) is questionable considering the adverse effects on gonads observed in rats, dog and hamster during the subchronic/chronic studies.	We do not have individual data on the dams to compare with data on those pups exhibiting cleft palate and anasacra. If the RAC rapporteur considers that this is relevant we will investigate further. Again we have included all relevant information in the proposal to allow RAC to make their deiciosn.	Cleft palate and anasarca were only observed at a dose level inducing excessive maternal toxicity, with >10% mortality. In accordance with the criteria, the effects found at such a dose level should not be considered for classification purposes. See further the response above to the Austrian comments.

Respiratory sensitisation

Date	Country / Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment

Other hazards and endpoints

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
11/10 /2011	Belgium /MSCA	Environment Based on the results of the aquatic toxicity test on the most sensitive species (14dEC50Lemna gibba = 2.6mg/l) the fact that the substance is considered as not rapidly degradable it is justified to classify, following the classification criteria of the 2nd ATP, as Aquatic chronic 2, H411. Furthermore, the substance shows a low potential to bioaccumulate (BCF <500). Based on the classification and labelling criteria in accordance with dir. 67/548/EEC, Tralkoxydim should be classified as N,R51/53. In conclusion : we agree with the proposed environmental classification by the UK MSCA. Some editorial or/and minor comments: 5.1.2.3 Simulation test Dakota system, sediment phase Table B.8.33, p.410 of DAR Volume 3, Annex B8 shows that the maximum for metabolite R173642 observed in the sediment phase is 0.8% AR by day 135 14C-cyclohexenone label instead of 4.5% of AR. R158378 peaked at 13.5% AR by day 135 based on 14C-phenyl label. 5.1.3 summary and discussion of degradation P.58 * conclusion on simulation study should be : tralkoxydim does NOT meet the criteria of 70% degradation in the aquatic environment within 28d (degradation half life >16d). * A readily test was not performed. The end conclusion on degradation is based on the results of simulation tests (biotic and abiotic degradation), so please modify "not readily biodegradable" to "not rapidly degradable" 5.4 Aquatic toxicity -It would be useful to give in the CLH-report the summary table B9.2.1 and B.9.2.1.2 on acute aquatic toxicity, included in the DAR. If no guideline is followed, more details on the test method used, are welcomed. -Aquatic plants : is the growth inhibition test on Lemna gibba a	 Thank you We have noted the typographical errors however, it was agreed that CLP dossiers will not be updated in addition to RCOMs following consulation. We agree and more recent dossiers include similar tables. The *Lemna gibba* study with tralkoxydim was static.	The support is noted. The necessary changes to sections 5.1.2.3 and 5.13 have been introduced (highlighted in grey).

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		static(CLH-report) or semi-static test(DAR)?		
12/10 /2011	Germany / MSCA	Acute toxicity: DE supports the proposed classification for tralkoxydim: Xn; R22 and Acute Tox 4 – H302, respectively. Repeated dose toxicity (STOT RE/R48): DE supports the proposed classification for tralkoxydim: Xn; R48/22 and STOT RE2 – H373, respectively.	Thank you for your comments.	The support is noted. However, where RAC supported the proposal for acute toxicity, it considered the classification for repeated dose toxicity a borderline case (see response to comments from Syngenta Crop Protection AG on this subject).
14/10 /2011	Finland / Finnish Safety and Chemicals Agency / MSCA	We support the proposed classification for Acute Tox. 4 and STOT RE 2, as well as the environmental classification.	Thank you for your comments	The support is noted. However, where RAC supported the proposal for acute toxicity and for environmental toxicity, it considered the classification for repeated dose toxicity a borderline case (see response to comments from Syngenta Crop Protection AG on this subject).