Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Tolclofos-methyl (ISO); *O*-(2,6-dichloro-p-tolyl) *O,O*-dimethyl thiophosphate

EC Number: 260-515-3
CAS Number: 57018-04-9

CLH-O-0000001412-86-266/F

Adopted

15 March 2019

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON TOLCLOFOS-METHYL (ISO); *O*-(2,6-DICHLORO-P-TOLYL) *O,O*-DIMETHYL THIOPHOSPHATE

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: tolclofos-methyl (ISO); *O*-(2,6-dichloro-p-tolyl) *O,O*-dimethyl thiophosphate
EC number: 260-515-3
CAS number: 57018-04-9
Dossier submitter: Sweden

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
13.09.2018	France	Sumitomo Chemical Agro Europe	Company-Manufacturer	1
Comment received				
Page 34 of CLH (Table 34, first column): the "In vitro mutagenicity testing of Tolclofos-methyl in the Salmonella typhimurium plate incorporation assay" referenced in RAR Vol.3 B.6.4.1/02, should be corrected with "TA102" instead of "TA120" (typo). Page 35 of CLH (Table 34): Three tests are in vivo experiments: In vivo chromosomal aberration test on bone marrow cells of mice, Micronucleus test in mice and Mutagenicity evaluation of S-3349 T.G. Lot No. 4 in the rat dominant lethal assay). Therefore they should be moved to Table 35 (Summary table of mutagenicity/genotoxicity tests in mammalian somatic or germ cells in vivo)				
Dossier Submitter's Response				
Agreed				
RAC's response				
Noted				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2018	Spain		MemberState	2
Comment received				
Tolclofos-methyl has a harmonised classification in Skin sens. 1, regarding health hazards. The substance was discussed at the Meeting of Technical Committee C&L on the Classification and Labelling of Dangerous Substances in Arona (21-24 September), 2004. In the report (ECBI/139/04 Rev. the Technical Committee C&L agreed to classify Tolclofos-methyl with R43. The skin sensitisation potential of tolclofos-methyl was assessed in two studies in the guinea pig (Buehler method and Guinea Pig Maximisation Test (GPMT). Tolclofos-methyl was found to be positive in the GPMT. The Buehler study was negative but the study was considered limited (few animals were used and the results of the preliminary investigations were not reported). In the study performed with tolclofos-methyl where Guinea Pig Maximisation Test was used, the induction concentration of 5 % (intradermal induction) and 25% (topical induction) resulted in a sensitisation rate of 35% after a challenge with 10% test substance. Thus, tolclofos-methyl should be classified as a skin sensitizer and fulfils the criteria for subcategorisation in category 1B (Guinea Pig Maximisation Test: ≥30% responding at >1% intradermal induction dose. The Spanish CA supports the proposal of the dossier submitter to change the current classification of mancozeb to Skin Sens 1B, H317.				
Dossier Submitter's Response				
Noted. (there seems to be a typing error in the last paragraph above, manozeb instead of tolclofos-methyl)				
RAC's response				
Noted. RAC also supports the DS proposal.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
11.09.2018	Germany		MemberState	3
Comment received				
Reduction in cholinesterase activity was observed in several studies in rats, dogs and mice at ranges just below 20%. This finding was discussed during Pesticides Peer Review 162 and the majority of experts agreed that this might not be relevant in the absence of neurotoxic effects. However, in principle, STOT RE can be based on "serious changes in biochemistry". Therefore we suggest to address this issue in the dossier.				
Dossier Submitter's Response				
Agreed. Reduction in cholinesterase activity were found in rats, mice and dogs. In the mouse, reductions above 20% could be found at a dose within the critical range of doses for Cat 2 classification. At PPR 162 meeting it has been argued that this effect was not				

considered severe enough for STOT-RE classification since no clinical signs occurred. However, indeed evidence of any consistent and significant adverse change in clinical biochemistry seems to be sufficient evidence for a STOT- RE classification according to the CLP Regulation 3.9.2.7.3. Thus classification with STOT-RE (H373) seems relevant.
RAC's response
RAC considers a statistically significant and dose- or time-related inhibition of acetylcholinesterase of ≥ 20% in brain (or in erythrocytes, as surrogate when no data on brain are available) to meet the criteria for classification, even when not accompanied by clinical signs. However, of all the available repeated dose studies, there is only one (the 9-months mouse study) where a ≥ 20% inhibition was observed at a dose level relevant for classification for STOT RE. In this study, the percentage inhibition of erythrocyte acetylcholinesterase activity was at the cut-off of 20%, in males only, and was accompanied by an increase rather than an inhibition in brain acetylcholinesterase activity. Overall, RAC considers the sole finding of a 20% reduction in erythrocyte acetylcholinesterase activity in one study in one sex only, without an inhibitory effect on brain acetylcholinesterase activity, insufficient evidence for classification.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
17.09.2018	France		MemberState	4
Comment received				
FR agrees with the classification and the M-factors proposed for Tolclofos-methyl.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
13.09.2018	France	Sumitomo Chemical Agro Europe	Company-Manufacturer	5
Comment received				
Page 140 of CLH (Table 71, line Scenedesmus subspicatus/Tolclofos-methyl): The statement that there is no information on the ErC50 for the algal study with Tolclofos-methyl is not correct, see our comment about page 156. Page 140 of CLH (Table 71, line Americamysis bahia Saltwater mysid/Metabolite ph-CH3): Reference to report number QW-0148 of acute toxicity study with mysid and metabolite ph-CH3 should be added (see page 156). Page 140 of CLH (Table 71): The following studies should be added to the reference column in the summary table: # Wirzinger and Strecker, 2017. Re-calculation of toxicity endpoints for acute effects of Tolclofos-methyl on Americamysis bahia based on geometric mean measured concentrations (QW-0171) # Wirzinger and Strecker, 2017. Re-calculation of toxicity endpoints for acute effects of the Tolclofos-methyl metabolite ph-CH3 on Americamysis bahia based on geometric mean measured concentrations (QW-0172) Page 156 of CLH, Scenedesmus subspicatus: The EU endpoint agreed with EFSA and EU				

RMS was ErC50 > 0.9 mg a.s./L (see EFSA conclusion of Tolclofos-methyl, EFSA Journal 2018, 16(1) Appendix A page 52). The test item was dissolved in solvent in order to increase the solubility of Tolclofos-methyl in the algal study. As a solvent was used, it is possible to achieve an endpoint for growth (ErC50) greater than the solubility limit for Tolclofos-methyl of 0.7 mg a.s./L. Sumitomo consider that this endpoint can also be used for the classification. Page 160 of CLH (Table 94, line Scenedesmus subspicatus/Tolclofos-methyl): The statement that there is no information on the ErC50 for Tolclofos-methyl is not correct, see our comment about page 170). Page 170 of CLH, Scenedesmus subspicatus: same comment as in page 156. Page 173 of CLH, section 11.8, 2nd paragraph: The first line contains an error and should be completed as follows: "Tolclofos-methyl can be classified as Aquatic Chronic 1 with an M-factor 1 (0.01<NOEC=<0.1 mg/L) …".
Dossier Submitter's Response
Agree that the ErC50 for Scenedesmus subspicatus/Tolclofos-methyl should be updated to >0.9 mg/L, which was the finally EU agreed value (EFSA conclusion). The statement on page 160 that there is no information on the ErC50 should be replaced with the agreed value, and the corresponding wordings on page 170 should be corrected accordingly. Agree that the reference to the Americamysis study by Shaw (2014b) in table 71 should be amended with the report number QW-0148, and that the references to the re-calculated toxicity endpoints based on geometric mean concentrations for tolclofos-methyl and ph-CH3 (QW-0171 and QW-0172, respectively) should be added to Table 71. Agree with the proposed correction of the typing error in the 2nd paragraph.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
11.09.2018	Germany		MemberState	6
Comment received				
We support the proposal of classification for environmental hazards as Aquatic acute 1 (H400), Aquatic chronic 1 (H410) and the acute/chronic M-factor of 1.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
17.09.2018	France		MemberState	7
Comment received				
FR: p.6-7: Physicochemical properties, Table 7 : purity of the test substance could be added for each property.				

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Dossier Submitter's Response
Agreed.
RAC's response
Noted