Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

azamethiphos (ISO); *S*-[(6-chloro-2-oxooxazolo[4,5-*b*]pyridin-3(2*H*)-yl)methyl] *O,O*-dimethyl thiophosphate

EC Number: 252-626-0
CAS Number: 35575-96-3

CLH-O-0000001412-86-290/F

Adopted

13 June 2019

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON AZAMETHIPHOS (ISO); S-[(6-CHLORO-2-OXOOXAZOLO[4,5-B]PYRIDIN-3(2H)-YL)METHYL] 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: azamethiphos (ISO); *S*-[(6-chloro-2-oxooxazolo[4,5-*b*]pyridin-3(2H)-yl)methyl] *O,O*-dimethyl thiophosphate
EC number: 252-626-0
CAS number: 35575-96-3
Dossier submitter: United Kingdom

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
23.11.2018	Germany		MemberState	1
Comment received				
The ATE value for Acute Tox. 3; H331 should be consistently given as "ATE (inhalation) 0,5 mg/l (dusts or mists)".				
Dossier Submitter's Response				
Noted. Thank you for your comment.				
RAC's response				
Noted - Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
05.12.2018	France		MemberState	2
Comment received				
Identity FR: the minimum purity for the active substance set in the CAR is 970g/kg, which is not in accordance with the degree of purity reported in this section				
Dossier Submitter's Response				
The minimum purity has been updated to 98% in the CAR as specified in the CLH report.				
RAC's response				
The purity in all studies included in the CLH report is 96.4 %, except for the dietary carcinogenicity studies in rat and mouse, for which the purity is 95.6 % or 94.2 %, and for the rat COMET assay the purity is 99.68 %, while for some other studies the purity is not indicated.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
31.10.2018	Denmark		MemberState	3

Comment received

Acute Tox. 4;H302.
The product has been tested and a LD50 value between 300-2000mg/kg have been set.
In the CLH report this have been converted to an ATE = 500 mg/kg.
We would suggest that the converted ATE is not assigned in Annex VI to CLP.
Reasoning: If the converted value is set in annex VI, the value of 500mg/kg is mandatory, thus is companies have more specific results, they are not allowed to use this.
If you omit the converted ATE, companies without test data, should still use the same value, based on the current legislation. CLH section 10.1.1

Acute Tox. 4;H332.
The product has been tested and a LC50 value between 0,5-1,0mg/l have been set.
In the CLH report this have been converted to an ATE = 0,5 mg/l.
We would suggest that the converted ATE is not assigned in Annex VI to CLP.
Reasoning: If the converted value is set in annex VI, the value of 0,5mg/l is mandatory, thus is companies have more specific results, they are not allowed to use this.
If you omit the converted ATE, companies without test data, should still use the same value, based on the current legislation. CLH section 10.3.1

Dossier Submitter's Response

Thank you for your comments.

The LD50 derived from the acute oral toxicity study was determined to be 500 mg/kg bw and the LC50 in the acute inhalation study was between 0.5-1.0 mg/lg. These values were therefore used to support the proposed ATE values as noted in the CLH report. We note your comments and agree that an alternative approach would be to not define the ATE values but allow suppliers to determine the appropriate ATE values based on the information available to them. However, this could lead to confusion with suppliers applying differing values. Consideration should be given to when it is appropriate to define an ATE, where the only data available are a range of values.

RAC's response

RAC agrees with the DS' response, in addition, please refer to the current CLP guidance from July 2017. In section 1.5.3 "Harmonised ATE values" it states: "From 2016 harmonised Acute Toxicity Estimates (ATE) may be included in Annex VI of CLP. These values have to be used, just as any other harmonised item. ATEs are one way of expressing acute toxicity (see Annex I to CLP, 3.1.2.1)."

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
23.11.2018	Germany		MemberState	4

Comment received

Potency by EC3 values could not be calculated from the study by van Otterdijk 2008 because SI values are even at the lowest concentration of 10 % up to the limit, not significantly increasing with 25 % and 50 % Azamethiphos. No subclassification into 1A or 1B is possible on the basis of these data.

Dossier Submitter's Response
Thank you for your comment.
RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
05.12.2018	France		MemberState	5
Comment received				
FR position: We agree with the environmental assessment of the CLH report.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you.				

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
23.11.2018	Germany		MemberState	6
Comment received				

Section 8.7 Self-reactive substances

The conclusion on non-classification for self-reactive substances because there are no chemical groups present in the molecule associated with explosive or self-reactive properties is not supported by experts of DE CA.
The classification procedures for self-reactive substances and mixtures need not be applied in accordance with the criteria given in section 2.8.4.2 of Annex I to Regulation (EC) No 1272/2008 if:
(a) There are no chemical groups present in the molecule associated with explosive or self-reactive properties. Examples of such groups are given in Tables A6.1 and A6.2 in Appendix 6 of the UN RTDG, Manual of Tests and Criteria; or
(b) For a single organic substance or a homogeneous mixture of organic substances, the estimated SADT for a 50 kg package is greater than 75 °C or the exothermic decomposition energy is less than 300 J/g. The onset temperature and decomposition energy can be estimated using a suitable calorimetric technique (see Part II, sub-section 20.3.3.3 of the UN RTDG, Manual of Tests and Criteria).

However, Azamethiphos has chemical groups present in the molecule which are associated with explosive or self-reactive properties. Information can be found in Bretherick's Handbook of Reactive Chemical Hazards: A number of phosphate and thiophosphate esters are of limited thermal stability and undergo highly exothermic self-accelerating decomposition reactions which may be further catalysed by impurities. The potential hazards can be reduced by appropriate thermal control measures.

It has to be noted that for Azamethiphos the oxygen balance value is -88.9, which identifies the substance to be a potential explosive, as it is greater than the limit value of -200.

An experimentally study to determine the SADT in a 50 kg package was not performed. Additionally, classification may be made through the determination of the thermal

characteristics of the substance (Differential Thermal Analysis, Differential Scanning Calorimetry) which can provide data of the exothermic decomposition energy. The DSC should confirm that the exothermic decomposition energy is < 300 J/g and the onset of exothermic decomposition is < 500 °C, for the non-classification of the substance as a self-reactive.

Recommendation: Studies to determine the exothermic decomposition energy and if it is higher than 300 J/g also the SADT should be provided.

Section 8.10 Self-heating substances

Due to the low melting point of 90 °C the classification procedure for self-heating substances need not to be applied.
Justification for data waiving: The study does not need to be conducted because the substance is completely molten at 160°C.

Conclusion: Not classified - conclusive but not sufficient for classification.

Dossier Submitter's Response

Thank you for your comments.

The oxygen balance is greater than the value of -200 and is, therefore, within the region for potential explosive properties. However, the relatively high oxygen balance is considered to be due to the chloro-oxooxazolo pyridine and phosphorothioate group in the molecule and based on a consideration of the full structure is not considered to suggest the risk of explosivity.

With regards to self-reaction, it is noted that the structure does contain a thiophosphate ester moiety and that Brethericks refers to a number of phosphates and thiophosphates being of limited thermal stability.

The DSC shows a discrete exotherm (decomposition) between 175 – 200°C but the heat of decomposition is not provided. No further data are available.

It is the opinion of the dossier submitter that the available data do not support classification of the substance as a self-reactive substance. However, the conclusion may more appropriately be changed to not classified – data lacking or data inconclusive.

We agree that the substance is not classified as a self-heating substance. The conclusion may be updated as suggested.

RAC's response

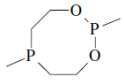
Thank you for your comment.
1. Azamethiphos does not contain a phosphite group (P(III)). Azamethiphos does not contain a thiophosphate group ($O(OR)_2$-P=S). Azamethiphos is a thioester (-S-P-$O(OCH_3)_2$).
2. Some thiophosphates and phosphates are thermally unstable and undergo highly exothermic self-accelerating decomposition reactions which may be further catalysed by impurities according to Bretherick's Handbook of Reactive Chemical Hazards.

This is a very general rule which includes all substances of P(III), P(V) and P(VI). The conclusion is valid mostly for compounds of P(III) as is shown in Appendix 6 of the UN

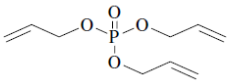
RTDG and P(VI). The check of all examples for self reactive substances of P(V) (see bellow, as presented in Bretherick's Handbook) could be also attributed to the additional self reactive group – azo, azid, peroxo, nitro… or to the reaction with active substance – chlorine, diazinon etc.

Examples from Bretherick's Handbook

Allyl phosphorodichloridite, 1165* – P(III) -
Bis(trimethylsilyl) phosphonite, 2607 – P(III)
O—O-tert-Butyl di(4-tolyl) monoperoxophosphate, 3757 – peroxo compound
O—O-tert-Butyl diphenyl monoperoxophosphate, 3706 - – peroxo compound
Diallyl phosphite (Di-2-propenyl phosphonite), 2450 – P(III)
Dibenzyl phosphite, 3651 – P(III)
Dibenzyl phosphorochloridate, 3643 - It is too unstable to be distilled, and the precursory phosphite also tends to decompose on distillation
Dibutyl hydrogen phosphite, 3080 – P(III)
Diethyl 4-nitrophenyl phosphate, 3323 - nitrophenyl
Diethyl 4-nitrophenyl thionophosphate, 3322 - nitrophenyl
Diethyl ethanephosphonite, 2567 – P(III)
Diethyl phosphite, 1727 – P(III)
Diethyl phosphorochloridate, 1675 - Presence of hydrogen chloride as impurity causes an uncontrollable exothermic reaction during preparation of diethyl phosphate from the title compound.
Dimethyl 2-chloro-4-nitrophenyl thionophosphate, 2955 - - nitrophenyl
Dimethyl 3-chloro-4-nitrophenyl thionophosphate, 2956 - - nitrophenyl
Dimethyl 4-nitrophenyl thionophosphate, 2974 - - nitrophenyl
Dimethyl ethanephosphonite, 1726 – P(III)
Dimethyl hydrazidophosphate, 0955 - hydrid
Dimethyl N,N-dichlorophosphoramidate, 0897 -
Dimethyl phosphoramidate, 0948 - in reaction with chlorine
O,O-Dimethyl S-methylcarbamoylmethyl phosphorodithioate, 2003 – dimethoate- aliphatic, accident, melting point 43 C, flash point 107
2,6-Dimethyl-1,3-dioxa-2,6-diphosphacyclooctane, 2543



Temperature above 120 cause explosion
Di(O—O-tert-butyl) ethyl diperoxophosphate, 3368 – peroxo compund
Diphenyl azidophosphate, 3483 - azid
Potassium O,O-diphenyl dithiophosphate, 3475 – in reaction with Arenediazonium salts
Pyrocatecholato(2-)(quinolin-8-olato-N,O)-trioxygenido(2-)phosphorus, 3671 - hexavalent phosphorus ozonide, stable at (-20 °C), exploded in contact with air or on warming to ambient temperature
Triallyl phosphate, 3178 – aliphatic, under distillation



Alkali-washed material, stabilised with 0.25% of pyrogallol, was distilled at 103 °C/4 mbar until slight decomposition began. The heating mantle was then removed and the still-pot temperature had fallen below its maximum value of 135 °C when the residue exploded violently [1]. The presence of solid alkali [2] or 5% of phenolic inhibitor is recommended, together with low-temperature high-vacuum distillation, to avoid formation of acidic decomposition products, which catalyse rapid exothermic polymerisation.
Trimethyl phosphate, 1314 – explode during distillation
Trimethyl phosphite, 1311 – P(III)
Trimethyl thiophosphate, 1312 – in reaction with chlorine
* - numbers as given in Bretherick's Handbook of Reactive Chemical Hazards Seventh Edition Volume 1

Additionally, the compound is stable on accelerated storage at 54 °C (Proposed Registration Decision (PRD2016-25), published by the Health Canada Pest Management Regulatory Agency for the product Salmosan Vet (50 % azamethiphos)).
RAC supports DS' proposal for no classification even without additional test data.

Date	Country	Organisation	Type of Organisation	Comment number
05.12.2018	France		MemberState	7
Comment received				
8.10 Self heating substances FR: no test has been provided to demonstrate that the active substance is not a self				

heating substance. The conclusion "data lacking" is not appropriate. At least a scientific case (or a test according to manual UN RTDG) should be provided by the applicant to confirm this point. 8.15 Corrosive to metals FR: no test has been provided to demonstrate that the active substance is not corrosive to metals. The conclusion "data lacking" is not appropriate. A demonstration using method C.1 described in manual UN RTDG or a scientific case should be provided by the applicant.
Dossier Submitter's Response
Thank you, we note the comments. The CLH report is based on the data available on the substance. Please see the response to comment number 6 also.
RAC's response
Thank you for your comment. 8.10. Self heating substances The classification procedure for self-heating substances need not to be applied, because the substance is completely molten at 160 °C as already commented by one MSCA. 8.15. Corrosive to metals Azamethiphos is a weak acid (pKa 2.2), pH of aqueous solution is 4-7, structurally, interaction with metals is not expected – corrosion toward metals is not expected.