Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Phenyl bis(2,4,6-trimethylbenzoyl)-phosphine oxide

EC Number: 423-340-5

CAS Number: 162881-26-7

CLH-O-0000001412-86-152/F

Adopted

9 June 2017

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ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON PHENYL BIS(2,4,6-TRIMETHYLBENZOYL)-PHOSPHINE OXIDE

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: Phenyl bis(2,4,6-trimethylbenzoyl)-phosphine oxide
CAS number: 162881-26-7
EC number: 423-340-5
Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
30.09.2016	Germany	GEELIO Umwelttechnologie GmbH	Company-Importer	1
Comment received				
We agree on the proposal to remove the harmonised classification of Aquatic Chronic 4 - H413.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
RAC does not support removing the classification. Please see the opinion for details.				

Date	Country	Organisation	Type of Organisation	Comment number
30.09.2016	Sweden		MemberState	2
Comment received				
The way that the method and results of the studies are presented in the CLH-report makes it difficult for the reader to evaluate the studies thoroughly and to judge if the conclusions made by the DS are acceptable. A higher level of detail is indeed desirable.				
Dossier Submitter's Response				
The DS acknowledges the comment by the Swedish MSCA. It is agreed that a higher level of detail should be provided in the CLH report. Therefore the methods and results of the two GMPTs are presented in more detail in Annex 1. Hereby an exptended version of table 9 and a new table showing results from individual animals are given, to enable an improved evaluation of the conclusions drawn.				
RAC's response				
Thank you for your comment.				

Expanded versions of results from two GPMT studies were submitted by the DS in Annex 1 were evaluation by RAC.

Date	Country	Organisation	Type of Organisation	Comment number
30.09.2016	France		MemberState	3
Comment received				
FR MSCA does not support the proposal to remove classification of Phenyl bis(2,4,6-trimethylbenzoyl) -phosphine oxide (CAS number: 162881-26-7) as Aquatic Chronic 4, H413.				
Dossier Submitter's Response				
See reponse to comment number 11.				
RAC's response				
RAC agrees with the Member State opinion.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
30.09.2016	France		MemberState	4
Comment received				
Although this section is not opened for comment, a discussion on potential developmental toxicity of this substance may be necessary based on the increased incidence of skeletal variations and malformations observed without maternal toxicity at high doses in the available prenatal developmental toxicity study in rat.				
Dossier Submitter's Response				
The DS acknowledges the comment by France. It is not agreed that a discussion on potential developmental toxicity is necessary as reproduction toxicity was not in the scope of the present CLH dossier.				
RAC's response				
Thank you for your comment but reproductive toxicity is not in the scope of the present CLH dossier				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
30.09.2016	Finland		MemberState	5
Comment received				
The FI CA does not agree with the proposed classification and labelling of phenyl bis(2,4,6-trimethylbenzoyl) -phosphine oxide as Skin Sens. 1A; H317. The proposal is based on a worst-case challenge response rates from two guinea pig maximization tests. Two GPMT:s OECD 406 are presented in the CLH report. Noted differences between the studies are strains, sexes and number of guinea pigs; vehicles; test concentrations and the handling of the light sensitive test substance during the study. The first GPMT was conducted under normal light conditions and the study report has no information on the possible light-induced degradation of the test substance. This raises a concern about the validity of the study. Therefore, the result which shows strong potency of skin sensitization should be carefully considered. Light-induced degradation or toxicokinetics are not described in the report, which increases the uncertainty. Very high				

positive reaction rate (90 %) after only 24 hours of exposure could indicate strong potency of skin sensitization of the degradation product. However, more detailed information is needed for interpretation of the results.

The second GPMT was performed under controlled light conditions and can be considered more reliable than the first GPMT. Compared to the first study, only males of another strain of guinea pig were used with half of the animal number, which is less than the test guideline recommendation. The DS uses a worst case assumption and a worst-case sensitization rate of 60 % to justify the classification for sub-category 1A. The DS has summed the positive animals from all time points and two equivocal test animals which yield 60 % of sensitization rate. The calculation of this value is very unclear. When looking at the results after each challenge concentration and time point, only one result is 60 % while others are below it. After 72 hours with a challenge concentration of 70 % including one test animal with inconclusive skin reactions, the positive result is 60 %. The highest unequivocal positive results (50 %) in this study are after 48 and 72 hours with a challenge concentration of 70 %. Without giving too much weight on the result of one equivocal test animal after observation period of 72 hours, it's the FI CA's view that, as the intradermal induction concentration was 1.0 %, the result of this study does not meet the criteria for sub-category 1A but could meet the criteria for sub-category 1B.

In the FI CA's view the results of the two studies should be assessed separately as such and not use an overall worst-case challenge response rate.

In conclusion, the FI CA does not support the proposed harmonised classification and labelling of phenyl bis(2,4,6-trimethylbenzoyl) -phosphine oxide as Skin Sens. 1A; H317.

Dossier Submitter's Response

The DS acknowledges the comment by Finland.

It is not agreed to change the proposed classification of the substance as Skin Sens. 1A; H317. However, based on the comment, it is proposed to clarify the justification for the classification proposal as shown in Annex 1 and as specified below.

Is is agreed that the lack of information on the possible light-induced degradation of the substance in the test performed under normal light conditions (CIBA-GEIGY, 1996) interferes with the validity and reliability of the study. The DS therefore exclude this study from decision on classification for the substance.

The DS recommends that the decision on classification should be based only on the study performed under controlled light conditions (Huntington Life Sciences, 1997). The DS consideres this study valid and reliable. The animal number is as recommended in OECD TG 406 (adopted 17.07.92) in section 13, as a minimum of 10 animals in the treatment group and at least 5 control animals have been used.

Results after challenge with 70% and 35% test substance concentrations and after 24, 48 and 72 h were calculated separately. The maximum sensitisation reaction observed was 60 % (6/10 animals with a positive reaction) at 72 h with 70% challenge concentration. Thus, in the DS view, the results of the study meet the criteria for sub-category 1A. Reactions (dryness and sloughing of the epidermis or dryness and sloughing and thickening of the epidermis) which were described as ± by the authors of the study have been interpreted as clear positive results according to recommendations in Schlede and Eppler, 1995. Thus, decision on classification was not based on a worst-case assumption but rather on results considered to be positive evidence of skin sensitisation.

Additional Reference
Schlede E and Eppler R, 1995, Testing for skin sensitisation according to the notification procedure for new chemicals: the Magnusson and Kligman test. Contact Dermatitis, 32:1-4.

RAC's response

Thank you for your comment.
RAC considers that people might be exposed to phenyl bis(2,4,6-trimethylbenzoyl) - phosphine oxide under normal light conditions. Consequently, RAC considers that results of the study by CIBA-GEIGY (1996c) performed under normal daylight and showing strong skin sensitising properties of the substance, or its potential metabolites formed by daylight irradiation, should be considered for classification.

Date	Country	Organisation	Type of Organisation	Comment number
30.09.2016	Sweden		MemberState	6

Comment received

To thoroughly evaluate the results of the studies it would help if the DS could give a background to the use of the substance, and detail the events following exposure of the substance to light. To our understanding, radicals may be formed following activation at/close to visible light, and the activated substance may therefore be more reactive than the original substance. It would be helpful if the DS would discuss this matter and how the difference in methodology between studies (one GPMT performed under normal light and one under protection from light) might influence the outcome.

The first GPMT study (CIBA-GEIGY, 1996) was performed under normal light. Irritancy reactions were detected during the dose selection study, and from information found at the dissemination site, it seems as if correct doses for induction and challenge were chosen. However, results from the dose selection study is not included in the CLH dossier. It would be helpful for the reader if they were. Results show that 80-90% of the animals had positive reactions to phenyl bis(2,4,6-trimethylbenzoyl)-phosphine oxide following intradermal induction at 0.5%. The Swedish CA agrees with the DS that the results from this study fulfills the classification criteria for Skin Sens 1A.

The second GPMT study (Huntington Life Sciences, 1997) is performed under protection from light. It seems as if the substance is a non-irritant (as indicated by the pretreatment with SLS in petrolatum), but the results and conclusions from the dose selection study is not included in the CLH dossier. Please consider including this information so that the reader could make a proper evaluation of the study design and results. We are puzzled as to why a concentration of 70% was used for dermal induction. If the substance is a non-irritant, a concentration of 100% is appropriate, unless there are issues with solubility and/or toxicity etc. If such were raised during dose selection, please clarify them in the CLH dossier. We also have questions regarding the assessment of positive reactions following the challenge. Please provide more detail on which animals reacted positively at which time point(s). Additional information on the re-assessment of sensitization of some animals is also desirable. The lack of information on dose selection makes it difficult to assess the validity of the study results. However, the results indicate that 50-60% of the animals responded at 1% intradermal induction dose. The skin sensitization frequency is borderline category 1A at that dose, according to the classification criteria.

Overall assessment of skin sensitization
Since it cannot be excluded that workers are exposed to the light-activated form of phenyl bis(2,4,6-trimethylbenzoyl)-phosphine oxide, we have based our assessment of its

sensitizing properties on the 1997 GPMT study where the substance was tested under normal light, and where 80-90% of the animals had positive reactions at 0.5% intradermal induction dose. Therefore, the Swedish CA agrees with the proposal to sub-categorize phenyl bis(2,4,6-trimethylbenzoyl)-phosphine oxide in category 1A.

Dossier Submitter's Response

The DS acknowledges the comment by Sweden.

Due to missing information on light-induced degradation of the substance in the GMPT study performed under normal light (CIBA-GEIGY, 1996) this study is considered to be of limited reliability. Hence, the DS propose to exclude this study from decision making on classification, but to consider the study as supporting material. The DS considers the GMPT study performed under safe light (Huntington Life Sciences, 1997) as reliable and valid and as sufficient to allow a definite decision on classification of the substance as Skin Sens 1A. Due to lack of data, the DS recommends to restrict the present CLH report to classification of the (original) substance phenyl bis(2,4,6-trimethylbenzoyl)-phosphine oxide but not to its light-induced degradation products. As data are considered to be sufficient for a classification of the "original" substance as Skin Sens 1A a similar level of protection is achieved for potential exposure of workers to the light-activated form of phenyl bis(2,4,6-trimethylbenzoyl)-phosphine oxide.

According to the authors of the GMPT study performed under safe light (Huntington Life Sciences, 1997), 70% of the test substance was the maximum practical concentration. The DS suggests to include this information in table 9 as shown in Annex 1. Moreover, it is proposed to add a new table 10 showing individual animal results of this test (Annex 1). The highest positive results considered unequivocal are leading to a 60% sensitisation rate of the animals (see table 10, Annex 1) after 72h with 70% challenge concentration and at 1% intradermal induction dose thus meeting the criteria for category 1A classification.

RAC's response

RAC agrees with the Member State opinion.

Date	Country	Organisation	Type of Organisation	Comment number
30.09.2016	France		MemberState	7

Comment received

Phenyl bis(2,4,6-trimethylbenzoyl) -phosphine oxide has an existing entry as Skin Sens. 1; H317. Sub-category 1A is proposed based on positive response higher than 60 % following intradermal induction at 0.5% and 1% in the two available GPMT studies (from 1996 and 1997, respectively).

In the second M&K study performed in 1997, positive reactions after both challenges (concentrations of 35 or 75%) were below 60% at 48h (and thus in line with subcategory 1B CLP criteria). It is not clear in the report and unusual to add positive additional animals after 72h. Therefore, with regard to sub-category, uncertainties remained.

Data available with other analogues benzoyl phosphine oxide show moderate skin sensitising potency. Indeed, for example, trimetylbenzoyldiphenylphosphine oxide (CAS no 75980-60-8) EC3 value from LLNA was 27% (SCCS/1528/14) and for ethyl phenyl(2,4,6-trimethylbenzoyl)phosphinate (CAS no 84434-11-7) it was 16% (from ECHA website).

Overall, we are in the opinion that the current harmonised classification Skin Sens. 1

H317 without subcategorisation should be retained due to uncertainties described above.
Dossier Submitter's Response
The DS acknowledges the comment by France. In the DS view positive reactions 72 h after removal of patches are covered by classification criteria in Table 3.4.3 of the CLP regulation and according to Eppler and Schlede (1995) data at observation time points 72 h after removal of patches are often not available due to usual termination of the study after 48 h but can be used for assessment if available. In the present case increasing reactions from 24 to 72h were obtained. The DS suggests to include this information and this reference in the CLH report as shown in Annex 1 (section 4.6.1.3). The DS concludes that results of the study, 60% sensitisation rate of the animals at 70% challenge concentration and at 1% intradermal induction 72 h after removal of the patches meet the criteria for category 1A classification. Reference: Schlede E and Eppler R, 1995, Testing for skin sensitisation according to the notification procedure for new chemicals: the Magnusson and Kligman test. Contact Dermatitis, 32:1-4.
RAC's response
Thank you for your comment. RAC considers that people might be exposed to phenyl bis(2,4,6-trimethylbenzoyl) -phosphine oxide under normal light conditions. Consequently, RAC considers that results of the study by CIBA-GEIGY (1996c) performed under normal daylight and showing strong skin sensitising properties of the substance, or its potential metabolites formed by daylight irradiation, should be considered for classification. The first GPMT conducted under normal light conditions shows strong potency for skin sensitization and is considered sufficient for a refined evaluation allowing the sub-categorisation. In fact, a second study also indicates a strong skin sensitising property of the substance.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
29.09.2016	United Kingdom		MemberState	8
Comment received				
We do not support removal of the Aquatic Chronic 4 proposal based on available data. We do not feel the available experimental bioaccumulation data are adequate for declassification based on the study deficiencies (e.g. not to GLP, non-standard guideline, only 1 test concentration, use of castor oil as vehicle and less fish than standard test guideline). While we note the test item was not detected in fish during the uptake period, it is not possible to determine a valid BCF would be <500 l/kg. We also note that a chronic toxicity to fish study is not available and it is unclear if effects would be observed as the most sensitive species is not known. On this basis Aquatic Chronic 4 should apply.				
Dossier Submitter's Response				
Thank you for your statements.				

In 2011 we supported the opinion of UK MSCA concerning the adequacy of the bioaccumulation study. But in MSC-22 the MSC "concluded that there is no need to request for repeating the bioaccumulation test in fish." (see: Draft MSC-22 Main conclusions and action points 14-02-12) and "reached unanimous agreement". As the MSC concluded that no repetition of the bioaccumulation study is necessary, we agreed to the industry proposal to delete Aquatic Chronic 4. In the same MSC meeting the "MSC discussed the need for long-term toxicity test to fish (Annex IX, 9.1.6) that was waived by the Registrant" and did not request a long-term toxicity test to fish.
RAC's response
RAC agrees with the Member State both in relation to bioaccumulation data and chronic fish study.

Date	Country	Organisation	Type of Organisation	Comment number
29.09.2016	Belgium		MemberState	9
Comment received				
We support the proposed removal of the environmental classification.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
RAC does not agree with declassification. Please see the opinion for further details.				

Date	Country	Organisation	Type of Organisation	Comment number
28.09.2016	Netherlands		MemberState	10
Comment received				
Page 21, Paragraph 5.3.1. Since the BCF study is the key study for revision the current classification of Aquatic Chronic 4, the summary of the BCF test should give more information. A BCF study with Cyrpinus carpio has been submitted. This study was found reliable Ri=2 with restrictions. The BCF was 5 and thus lower than the criterion of 500. Therefore, Phenyl bis(2,4,6-trimethylbenzoyl)-phosphine oxide cannot be classified as Aquatic Chronic 4. There are some questions on the BCF study that needs clarification. In the test summary it was not clear whether the steady state was reached after 28 days. Since only 4 analyses were available during the uptake phase (day 7, 14, 21 and 28) we wonder on which data the steady state was based. In addition, it is not clear whether the concentrations were measured during the study. Mean recovery rate was 94.8%. Is this the recovery of the analytical method or the mean recovery over the whole uptake phase? It should be made clear that the mean concentrations were high enough during the uptake phase. Nominal test concentration (1 µg/L test material) was below solubility of 2 µg/L test material and stock solution was prepared in castor oil (HCO-80). According to OECD 305, HCO-40 can be used as a dispersant. It is unknown whether HCO-40 and HCO-80 can be used as equivalents.				
Dossier Submitter's Response				
Thank you for your statements. As no substance was analytically detactable, no steady state could be reached. The mean recovery rate of 94.8% is in our view regarding the recovery of the analytical method. We				

are not aware if there are any disadvantages of the dispersant HCO-80 compared to HCO-40. PEG-80 Hydrogenated Castor Oil (HCO-80) is a polyethylene glycol derivative of Hydrogenated CastorOil (q.v.) with an average of 80 moles of ethylene oxide.
RAC's response
RAC agrees with the Member State regarding uncertainties in the bioaccumulation study. Regarding the use of Castor Oil there are different recommendations depending on which version of the OECD TG 305 is used. The BCF study is from year 1974. Using hydrogenated Castor Oil as dispersant has been allowed up to HCO-100 in the old OECD 305C guideline from year 1981 and in the revised guidelines 305 from years 1996 and 2012 only HCO-40 is allowed.

Date	Country	Organisation	Type of Organisation	Comment number
30.09.2016	France		MemberState	11
Comment received				
FR MSCA does not support the proposal to remove classification of Phenyl bis(2,4,6-trimethylbenzoyl) -phosphine oxide (CAS number: 162881-26-7) as Aquatic Chronic 4, H413 According to data presented in the dossier the substance exhibits a poor water solubility below to 0.1 mg/L and is not ready biodegradable, only 1% of biodegradation was reported after 28 days (OECD 301B : Ready biodegradability-CO2 evolution) and no biodegradation was observed in a modified MITI test (OECD 301C). Furthermore, the log Kow of 5.8 at 22°C meet the CLP criterion (log Kow>4) indicating a potential of bioaccumulation. Concerning aquatic toxicity tests, acute data are available for three trophic levels (fish, aquatic invertebrates and aquatic algae) and information on long term test is available only for Daphnia magna. No toxicity effects were observed until the limit solubility of the substance. Regarding to the study of bioaccumulation, we understand that this kind of substance with low water solubility and high log Kow are difficult to assess. However, we have uncertainties about this study. Thus, we are of the opinion that classification "Aquatic Chronic 4" should be remained.				
Dossier Submitter's Response				
Thank you for your statements. We are aware of some uncertainties of the bioaccumulation study. But in MSC-22 the MSC "concluded that there is no need to request for repeating the bioaccumulation test in fish." (see: Draft MSC-22 Main conclusions and action points 14-02-12) and "reached unanimous agreement". As the MSC concluded that no repetition of the bioaccumulation study is necessary, we agreed to the industry proposal to delete Aquatic Chronic 4. In the same MSC meeting the "MSC discussed the need for long-term toxicity test to fish (Annex IX, 9.1.6) that was waived by the Registrant" and did not request a long-term toxicity test to fish.				
RAC's response				
RAC agrees with the Member State's concerns.				