Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide

ECHA/RAC/CLH-O-0000001405-81-01/A2

Adopted

27 October 2010

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPSAL ON DIPHENYL(2,4,6-TRIMETHYLBENZOYL)PHOSPHINE OXIDE

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: diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide
CAS number: 75980-60-8
EC number: 278-355-8

General comments

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
22/04/2010	Netherlands / RIVM Bureau REACH / Member State	Please include page numbers Please replace 'EU criteria' with '67/548/EEC criteria'. Please replace 'GHS' with 'EC 1272/2008'	Done Done Done	We note that the changes have been implemented as requested.
14/05/2010	Portugal / Maria do Carmo Palma / Member State	Considering the present proposal, we agree to establish a harmonised classification and labelling for Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide. The proposed classification and labelling fulfills the criteria established both in CLP Regulation and 67/548/EEC Directive (health). Therefore, we support this proposal.	Agree.	Support for the proposed classification is noted.

Carcinogenicity

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Mutagenicity

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
22/04/2010	Netherlands / RIVM Bureau REACH / Member State	Page 15: Second study: Please specify "Initiator 554". In addition, please mention whether controls were included in this study. Page 17: Summary and discussion: Please include that only in vitro data were available. We agree with the proposed classification	Initiator 554 is a brand name used for diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide and is included in the table of synonyms on page 4. The fact that controls were included is already mentioned. Done.	This trade name is previously mentioned in the table of synonyms and controls are mentioned in the study summary. We note that the changes have been implemented as requested. Support for the proposed classification is noted.

Toxicity to reproduction

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
19/04/2010	France / AFSSET / Member State	In the first oral (gavage) 28-day study in rats, all males from the highest dose group (750 mg/kg/d) showed small testes but it is not known if these results were significant or not. Furthermore, only one male in the satellite 750 mg/kg/d group		We agree; the weight of available evidence from the repeated dose toxicity studies supports the finding that the testes are the target organ.

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		showed small testes. The results of the second oral (gavage) 28-day study in rats don't report the above stated effects on the testes. So, the oral 28-day studies alone are not sufficient for classification purposes. In the first oral (gavage) 90-day study in rats, males in the 300 and 1000 g/kg/d groups showed small testes and atrophy of the testicular parenchyma but they didn't exhibit reduced spermiogenesis. Whereas no clear dose-response relationship was observed with regard to relative testes weights and grading of the testicular atrophy, another 90-day study reported the above mentioned effects at the only tested dose and confirms that testis are a target organ of this substance. It cannot be excluded that oral gavage may have been a bolus effect as no diet-study could be performed for palatability reasons. However, gavage is an appropriate route of exposure for identification of reproductive hazard and the results of the gavage studies are considered relevant for classification purpose. Hair loss, ptosis, diuresis and abdominal distension associated to small testes reported in the first 28-day study could be		The possibility of a bolus effect cannot be excluded, but we agree that the studies presented are relevant for classification. It is a plausible that there may be a link between hypercorticism and the observed effects in the testes. A number

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		related to hypercorticism in rats. Likewise, lesions on the hairless skin of the extremities and scale formation on the ears for both males and females observed in the first 90-day study could be related to the resulting hormonal disturbance. In humans, the excess of cortisol may affect libido and induce impotence, amenorrhoea / oligomenorrhea, infertility. In particular, in males, increased plasma cortisol may depress LH secretion and cause secondary testicular dysfunction. The clinical signs related to hypercorticism observed in rats may therefore be consistent with the testicular effects observed in the 90-day studies and support that reproductive organs are affected by diphenyl(2,4,6 trimethylbenzoyl)phosphine oxide. Taking into account the decrease of relative weights of testes associated to diffuse testicular atrophy in rats in oral (gavage) 90-day studies, we agree with the proposed classification of diphenyl(2,4,6 trimethylbenzoyl)phosphine oxide as Repro. Cat. 2 (CLP) and Repro. Cat. 3, R62 (67/548/EEC).	Agree.	of clinical signs could support the occurrence of hypercorticism. However the expected haematological effects such as increased haemoglobin and red cell blood content, reduced white blood cell number and dimunition of lymphoid tissues (thymus, spleen and lymph nodes) were not observed. In the absence of additional data, this link cannot be confirmed. Support for the proposed classification is noted.
22/04/2010	Netherlands / RIVM Bureau REACH / Member State	Page 18: Summary and discussion: It is stated that classification with Cat. 1B (EC 1272/2008 criteria), requires demonstration of the impairment of		The dossier submitter indicates that classification as Repr. 2 (EC No. 1272/2008) is warranted because lesions of the testes is a valid but only

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		fertility in in vivo studies, and that although the evidence for testes lesions is clear, this is not enough for classification with 1B, since it may be an indirect indicator. However, according to GHS, classification with 1B requires only "clear evidence of an adverse effect on sexual function and fertility …not considered a secondary non-specific consequence of other toxic effects". We agree that it is not clear what the eventual effect on fertility will be. However. Paragraph 3.7.1.3 of Regulation EC 1272/2008 includes alterations of the (fe)male reproduction system as adverse effect on sexual function and fertility. Therefore, the observed atrophy of the testes could be enough for classification with Cat 1B (depending on effects being primary or secondary). Page 17/18: Summary and discussion: Please add argumentation whether the testis lesions may be secondary to other toxic effects observed, such as for instance anaemia (shown by reduced Hb, MCV and MCH in the first 28 day study).	Hematological effects such as reduced haemoglobin and hematocrit were observed at concentrations that also caused atrophy of the testes. However, not significantly enough to qualify as anaemia. As France noted, it cannot be excluded that the observed atrophy is due to hypercorticism and thus, may be a secondary effect.	an indirect indicator of reduced fertility. However as the Netherlands indicates, findings judged likely to impair reproductive function, that are not considered a secondary non-specific consequence of other toxic effects, may be used as a basis for classification. The justification for classification as Repr. 2 has been strengthened in the background document and draft opinion. We agree with Germany, the effects observed are not considered significant enough to indicate anaemia.
14/05/2010	Denmark / Peter Hammer Sørensen / Danish EPA / National	The Danish EPA aggress with the proposal by Germany for the classification of diphenyl(2,4,6-	Agree.	Support for the proposed classification is noted.

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	Authority	trimethylbenzol)phosphine oxide, cas. No. 75980-60-8. The classification for fertility caused by testicular atrophy were seen in several studies including an initial 28-day study in Sprague-Dawley rats, a 90-day study with Wistar rats and a confirmatory 28-day study in conjunction with a 90-day study. All studies show significant presences of testicular atrophy and clear evidence for testes lesions. However, the studies only indicate effects on fertility as no reproductive study is submitted. The classification Repro. Cat. 3; R62 is appropriate.		

Respiratory sensitisation

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Other hazard classes

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