Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling at Community level of

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

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

Adopted

27 October 2010

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OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT COMMUNITY LEVEL

In accordance with Article 37(4) of the Regulation (EC) No 1272/2008 (CLP Regulation), the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling of

Substance Name: ***diphenyl(2,4,6-trimethylbenzoyl) phosphine oxide***

EC Number: ***278-355-8***

CAS Number: ***75980-60-8***

The proposal was submitted by ***Germany***
and received by RAC on ***31 March 2010***

	Directive 67/548/EEC (criteria)	CLP Regulation (EC) No 1272/2008
Current entry in Annex VI CLP Regulation	no entry (Table 3.2)	no entry (Table 3.1)
Current proposal for consideration by RAC	Repr. Cat. 3; R62	Repr. 2 - H361f
Resulting harmonised classification (future entry in Annex VI CLP Regulation)	Xn; R62	Repr. 2 - H361f

PROCESS FOR ADOPTION OF THE OPINION

Germany has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/consultations/harmonised_cl/harmon_cl_prev_cons_en.asp*** on 31 March 2010. Parties concerned and MSCAs were invited to submit comments and contributions by 14 May 2010.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: ***Yvonne Mullooly***
Co-rapporteur, appointed by RAC: ***Andrew Smith***

The opinion takes into account the comments of MSCAs and parties concerned provided in accordance with Article 37(4) of the CLP Regulation.

The RAC opinion on the proposed harmonised classification and labelling has been reached on ***27/10/2010,*** in accordance with Article 37(4) of the CLP Regulation, giving parties concerned the opportunity to comment. Comments received are compiled in Annex 2.

The RAC Opinion was adopted by ***consensus.***

OPINION OF RAC

The RAC adopted the opinion that ***diphenyl(2,4,6-trimethylbenzoyl) phosphine oxide*** should be classified and labelled as follows:

Classification & Labelling in accordance with the CLP Regulation:

Classification: Repr. 2 - H361f Suspected of damaging fertility by causing atrophy of the testes.

Specific concentration limits: None

M-factors: None

Notes: None

Labelling: GHS08; Wng; H361f.

Classification & labelling in accordance with Directive 67/548/EEC

Classification[1]: Repr. Cat. 3; R62

Specific concentration limits: None

Notes: None

Labelling: Xn; R62; S(2) – 22 - 36/37.

SCIENTIFIC GROUNDS FOR THE OPINION

The opinion relates only to those hazard classes that have been reviewed in the proposal for harmonised classification and labelling, as submitted by *Germany*.

[1] This section should reflect all relevant entries for the C&L: classification, R-phrases, S-phrases, concentrations limits, nota.

Reproductive Toxicity

Multi-generation studies investigating the potential effects of diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide on fertility are not available.

Repeated dose toxicity studies reporting toxicity data on the testes are available. In the first 28-day study, male rats treated at the high dose (750 mg/kg bw/day) demonstrated reduced testes size, microscopically identified as testicular atrophy. Grading indicated increased severity of testicular atrophy at the high dose, although low-level atrophy was reported in the low- (50 mg/kg bw/day) and mid-dose (250 mg/kg bw/day) treated males. Testicular atrophy was also observed in the satellite group (750 mg/mg bw/day) at the end of the 14 day observation period. No testicular effects were noted in the second 28-day study, in which rats were dosed at 1000 mg/kg bw/day. In the first 90-day study, decreased absolute and relative testes weight, as well as diffuse atrophy of the testicular parenchyma and edema was observed in the mid- (300 mg/kg bw/day) and high-dose (1000 mg/kg bw/day) groups. The second 90-day study conducted at 1000 mg/kg bw/day in ten male rats, reported slight to severe diffuse atrophy (mostly bilateral) of the seminiferous tubules in the testes of all animals, edemas in four cases, as well as a minimal to slight hyperplasia of the Leydig cells. The epididymes were reduced in size and histopathology revealed oligo- to azoospermia. The weight of the available evidence supports the finding that the testes are a target organ for diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide in rat. The effects observed could lead to reduced male fertility. Based on the data presented, a classification of Repr. 2 H361f is proposed. No data is available for female fertility.

During the public consultation support for the proposed classification was received from three Member States, with the fourth commenting Member State indicating possible classification as Repr. 1B. Two of these Member States suggested that the effects observed in the testes may be a non-specific secondary effect. However, the RAC felt more information was required to clarify the relevance of these effects for the male fertility endpoint.

There are a number of limitations with the data set used for classification. There are no data available to show that the observed effects in the testes would lead to reduced male fertility or how severe that impact on fertility would be. The effects observed in the testes in the first 28-day study are not replicated in the second 28-day study. Diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide is administered by oral gavage in all the repeated dose toxicity studies and therefore, it cannot be excluded that the effects observed may have been due to a bolus effect. Furthermore, the use of the limit dose (1000 mg/kg bw/day) alone in the second 28- and 90-day studies means that no dose-response information can be obtained.

According to the CLP classification criteria (E.C. No. 1272/2008) substances classified in Category 2 for reproductive toxicity demonstrate an adverse effect on sexual function and fertility. From the available data it can be concluded that the target organ for diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide in rat is the testes. The lesions observed include testicular atrophy and edema, as well as oligo- and azo-spermia demonstrated in the second 90-day study. These adverse effects occur in the absence of significant generalised toxicity. However, due to the limitations discussed above, the evidence is not sufficiently convincing to place the substance in Category 1 and so classification as Repr. 2 is recommended. Also, according to the classification criteria of 67/548/EEC, classification with Category 2 requires demonstration of the impairment of fertility in *in vivo* studies, therefore because clear evidence for testes lesions is a valid but nevertheless only indirect indicator that diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide may lead to reduced fertility, classification with Repr. Cat. 3; R62 is appropriate.

During discussion of the dossier, RAC considered the alternative possibility of classification as Repr 1B (under CLP). However, it was concluded that the effects observed were not severe enough to warrant this classification, taking into account the lack of a consistent effect on the testes across all four repeat dose studies.

Additional information

The Background Document, attached as Annex 1, gives the detailed scientific grounds for the Opinion.

ANNEXES:

Annex 1	Background Document (BD)[2]
Annex 2	Comments received on the CLH report, response to comments provided by the dossier submitter and rapporteurs' comments (excl. confidential information)

[2] The Background Document (BD) supporting the opinion contains scientific justifications for the CLH proposal. The BD is based on the CLH report prepared by a dossier submitter. The original CLH report may need to be changed as a result of the comments and contributions received during the public consultation(s) and the comments by and discussions in the Committees.