Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

phosphine

EC Number: 232-260-8
CAS Number: 7803-51-2

CLH-O-0000001412-86-251/F

Adopted

30 November 2018

30 November 2018

CLH-O-0000001412-86-251/F

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

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

Chemical name: **phosphine**

EC Number: **232-260-8**

CAS Number: **7803-51-2**

The proposal was submitted by **France** and received by RAC on **27 November 2017.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

France 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/harmonised-classification-and-labelling-consultation/*** on **12 February 2018**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **13 April 2018**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Helena Polakovicova**

Co-Rapporteur, appointed by RAC: **Ruth Moeller**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **30 November 2018** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	015-181-00-1	phosphine	232-260-8	7803-51-2	Flam. Gas 1 Press. Gas Acute Tox. 2 * Skin Corr. 1B Aquatic Acute 1	H220 H330 H314 H400	GHS02 GHS04 GHS06 GHS05 GHS09 Dgr	H220 H330 H314 H400			U
Dossier submitters proposal	015-181-00-1	phosphine	232-260-8	7803-51-2	**Remove** Acute Tox. 2 * **Add** Acute Tox. 1	**Retain** H330	**Retain** GHS06	**Retain** H330		**Add** Inhalation: ATE = 11 ppmV (gases)	
RAC opinion	015-181-00-1	phosphine	232-260-8	7803-51-2	**Remove** Acute Tox. 2 * **Add** Acute Tox. 1	**Retain** H330	**Retain** GHS06	**Retain** H330		**Add** Inhalation: ATE = 10 ppmV (gases)	
Resulting Annex VI entry if agreed by COM	015-181-00-1	phosphine	232-260-8	7803-51-2	Flam. Gas 1 Press. Gas Acute Tox. 1 Skin Corr. 1B Aquatic Acute 1	H220 H330 H314 H400	GHS02 GHS04 GHS06 GHS05 GHS09 Dgr	H220 H330 H314 H400		Inhalation: ATE = 10 ppmV (gases)	U

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Phosphine is used as an insecticide under Regulation (EC) No 1107/2009, as an industrial chemical in semiconductor products and for the manufacture of electrical, electronic and optical equipment.

Phosphine already has an entry in Annex VI of Regulation (EC) No 1272/2008 (CLP) as Press. Gas; Flam. Gas 1 (H220); Skin Corr. 1B (H314); Acute Tox. 2* (H330); Aquatic Acute 1 (H400). The current harmonised classification of phosphine is transposed from that under the Dangerous Substance Directive (DSD) as F+; R12, R17, T+; R26, C; R34, N; R50.

The scope of the CLH proposal was to re-evaluate the existing minimum classification for acute inhalation toxicity in order to comply with the CLP criteria. The need for revision was considered justified by the Dossier Submitter (DS) because of the wide use of this substance in fumigation activities leading to cases of (sub)fatal accidents and because of the European plan for better control occupational risks for workers manipulating fumigated products. In addition, in the RAC opinions on aluminium phosphide (AlP) and trimagnesium diphosphide (Mg_3P_2), it was recommended that *"According to RAC, phosphine should be reclassified into acute inhalation toxicity category 1, having in mind that the LC_{50} values for phosphine from three studies are in a range between 11 – 51 ppm, well below the guidance values of 100 ppm for acute inhalation toxicity hazard category 1 for toxic gases".*

The CLH dossier is based on the available data in the REACH registration dossier for phosphine, on the RAC opinions on AlP and Mg_3P_2 (ECHA, 2011a,b), and on the draft assessment report on phosphine (DAR, 2010).

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute inhalation toxicity

Summary of the Dossier Submitter's proposal

Eight animal studies were presented in the CLH dossier. Roy (1998), Shimizu *et al*. (1982) and Waritz and Brown (1975) had been assessed in the RAC opinions for harmonised classification and labelling for acute inhalation toxicity of AlP and Mg_3P_2 (ECHA, 2011 a, b). Nachreiner and Dodd (1986) and Newton (1991) had been assessed in the draft assessment report (DAR) (2010) of phosphine. Newton (1993), Muthu *et al.* (1980) and Omae *et al.* (1996) were published studies for acute inhalation toxicity of phosphine, the latter being the only acute inhalation study for phosphine in mice.

The DS considered Shimizu *et al.* (1982) and Muthu *et al.* (1980) as unreliable, and the rest as acceptable studies. The DS did not determine the key study for the acute inhalation toxicity of phosphine.

In five studies (Roy (1998), Omae *et al.* (1996), Waritz and Brown (1975), Nachreiner and Dodd (1986); Muthu *et al.* (1980)), the LC_{50} values ranged from 11 ppm (Waritz and Brown, 1975) to 57 ppm (Nachreiner and Dodd, 1986) and they were thus considered by the DS to fall into classification category 1 for gases ($LC_{50} \leq 100$ ppm). Of these studies only Muthu *et al.* (1980) was considered unreliable by the DS due to an unusual protocol and insufficient information.

In two studies (Newton 1991 and 1993), no LC_{50} values had been derived by the study authors, but according to the DS the results of these studies were overall in line with the results of other available studies. In Newton (1993), the applied phosphine concentrations were too low for determining whether the LC_{50} would have fallen within the CLP criteria for category 1 (LC_{50} > 11 ppm). In Newton (1991), 50% mortality was obtained at the highest concentration of 28 ppm, and therefore according to the DS the LC_{50} could be set at 28 ppm for this study.

The highest LC_{50} value in rats, 204/179 ppm for males/females, respectively, was published in Shimizu *et al.* (1982) falling into category 2 of acute toxicity, however this LC_{50} was derived for a 1-hour exposure and the study was not considered sufficiently reliable by the DS.

The DS acknowledged some deficiencies in all the available studies and proposed to classify phosphine as Acute Tox. 1 (H330) based on a weight of evidence approach, considering that in the majority (5/7) of these studies, the LC_{50} value was below the limit for the classification category 1 for gases (100 ppm/V). According to the DS, this was further supported by the RAC opinions on AlP and Mg_3P_2, which recommended to update the classification of phosphine as Acute Tox. 1 (H330).

For the classification of mixtures containing phosphine, the DS proposed the acute toxicity estimate (ATE) value of 11 ppm, which was the lowest LC_{50} value for a 4-hour exposure obtained from the Waritz and Brown (1975) study, and which had been considered for the classification of metal phosphides by RAC. Considering uncertainties of the database, it was preferred to select the lowest LC_{50} value available.

Comments received during public consultation

Comments on acute inhalation toxicity were received from two Member States Competent Authorities (MSCAs). Both supported the proposal for the classification of phosphine as Acute Tox. 1; H330 (fatal if inhaled).

One of these MSCAs considered an ATE value > 11 ppm reasonable, taking into account reliability, relevance and completeness of the available studies. The MSCA noted that the dose levels in Waritz and Brown (1975) that had been used as the basis for the proposed ATE value of 11 ppm, were not reported. In addition, even though the study by Waritz and Brown (1975) had been considered in the RAC opinion for e.g. aluminium phosphide, the RAC opinion contained only three acute inhalation toxicity studies as references and the classification was derived for dust, while the current CLH dossier contained a larger selection of studies and the classification was derived for gas. The MSCA also noted that the proposed ATE value was missing from the classification table. The DS agreed with the MSCA about the quality of the studies, but defended the choice of the lowest LC_{50} value as the ATE value.

Assessment and comparison with the classification criteria

The CLH report contains eight acute inhalation toxicity studies that are summarised in the Table below.

Table: *Summary of the acute inhalation toxicity studies with phosphine*

Study	Test substance	Dose level/ duration of exposure	Results	Reference
US EPA guideline § 81-3, GLP Sprague-Dawley rats 5/sex/dose whole body, 14 days recovery period **Acceptable** (DAR (2010))	1.03% PH_3 in nitrogen	9-19-22-35-55-64-109 ppm 4h	No mortalities at 9,19, 22 and 35 ppm; 3/10 animals died at 55 ppm; 9/10 animals died at 64 ppm; 10/10 animals died at 109 ppm **LC_{50} : 57 ppm** (M/F) (0.08 mg/L), with 95% confidence interval of 49 to 66 ppm	Nachreiner, D.J., Dodd, D. E. (1986)
US EPA guideline § 81-3, GLP Rat Sprague-Dawley 1st part: 5/sex/dose 2nd part: 10 males/dose whole body **Acceptable**	1% PH_3 in nitrogen	1st part 0-1.3-6-28 ppm 2nd part: 0-3.1-10-18 ppm 6h	1st part: **50% mortality observed at 28 ppm.** 2nd part: No mortalities occurred up to 18 ppm **LC_{50} was not calculated, but 50 % mortality at 28 ppm.**	Newton, P.E. (1991)
No guideline, Non GLP Wistar Rats 5/sex/dose head only, 7 days recovery period **Acceptable**	PH_3 developed from AlP (technical)	0-15.4-26-47 ppm Note: The method of measurement was not very well documented (RAC (2011, a,b) 4 h	1/10 animals (M/F) died at 15.4 ppm; 3/10 animal (M/F) died at 26 ppm; 8/10 animals (M/F) died at 47 ppm **LC_{50} : 34.6 ppm (M/F)**	Roy, B.C. (1998)
US EPA guideline § 81-3, GLP Rat Fisher 344 15/sex/dose whole body 14 days recovery period **Acceptable**	1.06 % PH_3 in nitrogen	0-2.4-4.9-11 ppm (mean analytical exposure level) 6h	**No mortalities occurred.** **LC_{50} : >11 ppm (>0.016 mg/L)**	Newton, P.E. (1993) (Published)
Similar to OECD 403, Non GLP Rat Sprague-Dawley, 10/sex /dose, whole body 14 days recovery period **Not reliable** (no data for concentration measurement)	PH_3 generated from Mg_3P_2	150-165-182-200-242 ppm 1h 4h (calculated with Haber´s law)	No mortality at 150 ppm; 3/10 (F) and 0/10 (M) died at 165 ppm; 6/10 (F) and 1/10 (M) died at 182 ppm; 10/10 (F) and 4/10 (M) died at 200 ppm **LC_{50} (1h): 204/179 ppm (M/F)** (0.29/0.25 mg PH_3/L air (M/F) **LC_{50} (4h) calculated with Haber´s law: 51/45 ppm (M/F)** equivalent to 0.072/0.063 mg PH_3/L air	Shimizu, Y., Ogawa, Y. and Tokiwa, K. (1982)

Study	Test substance	Dose level/ duration of exposure	Results	Reference
Similar to OECD 403, Non GLP Rat Charles River CD, 6/male /dose, whole body **Acceptable**	PH_3 diluted in nitrogen	Dose levels not reported 4h	**LC_{50} : 11 ppm (M) equivalent to 0.015 mg PH_3/L air**	Waritz R.S. and Brown R.M. (1975)
Similar to OECD 403, GLP not specified Mouse ICR (ChR) 10/males/dose, whole body 14 days recovery period **Acceptable**	99.995% PH_3 diluted in highly purified nitrogen	1st experiment – 1h: 17.2-25.1-31.7-41.6-59.2 ppm 2nd experiment – 4h: 22.5-26.5-33.4-45.5-66.9 ppm 4h	1st experiment: no mortality occurred, **LC_{50} (1h) > 59.2 ppm** 2nd experiment: No mortality at 22.5 and 26.5 ppm; all animals died within 12 hours after completion of exposure at 66.9 ppm, within 2 days at 45.5 ppm and within 3 days at 33.4 ppm. **LC_{50} (4h) estimated: between 26.5 ppm and 33.4 ppm**	Omae K., Ishizuka C. and Nakashima H (1996) (Published)
No guideline Non GLP Rat Wistar, 6/females/dose, whole body **<u>Not reliable</u>** (Unusual protocol, no details on samples A and B, results difficult to interpret)	PH_3 generated from AlP pellets	Sample A: 20 ppm for 6h; 40 ppm for 4h; 27 ppm for 8h; 40 ppm for 6h Sample B: 33 ppm for 6h; 60 ppm for 4h; 33 ppm for 8h Concentration calculated: approx. 0,6 g yielding 0.2 g PH_3	The **LC_{50} values ranged from 28 ppm (27°C) to 33.3 ppm** (26,1°C) with related exposure period of 5.2 to 7.4 hours respectively for the product A and B.	Muthu M., Krishnakumari M.K., Muralidhara V. and Majumder S.K. (1980) (Published)

Overall, RAC agrees, in line with its previous opinion and with the DS, that the LC_{50} values derived for 4-hour exposure in rats vary between 11 ppm (males) and 57 ppm (males/females). One study was performed in mice, in which the LC_{50} value for a 4-hour exposure was estimated to be between 26.5 ppm and 33.4 ppm. The highest LC_{50} value of 204/179 ppm (males/females, respectively) for a 1-hour exposure was derived in the study by Shimizu *et al.* (1982), in which phosphine was hydrolysed from Mg_3P_2 and its concentration was calculated based on the amount of Mg_3P_2 added to a chamber with water. Due to the reported uncertainties, the study was considered as unreliable in the CLH report. Also RAC puts less weight on this study since the actual phosphine exposure might have been lower from the calculated one based on the actual hydrolysis rate. Therefore, the derived LC_{50} may result in underestimation of the toxicity.

According to the CLP criteria for classification of gases for acute inhalation toxicity category 1, the LC_{50} needs to be ≤ 100 ppmV. The majority of LC_{50} values derived from the different studies is well below this limit. **RAC agrees to classify phosphine as Acute Tox. 1; H330 (Fatal if inhaled) is warranted**.

The DS suggested an ATE value of 11 ppm for classification of mixtures containing phosphine based on the Waritz and Brown (1975) study, which gave the lowest LC_{50} value for a 4-hour

exposure. It is noted that for AlP and Mg_3P_2, RAC considered this study in support of classification for Acute Tox. 1; H330. However, a larger selection of studies is available to RAC for the hazard assessment of phosphine itself. RAC agrees that in general, the lowest available ATE value is selected for mixture classification, but another ATE value may be selected with expert judgement and a robust justification. RAC acknowledges that the Waritz and Brown (1975) study is the oldest study and that it has deficiencies because the tested dose levels have not been reported. Nachreiner and Dodd (1986) and Newton (1993) in rats provided LC_{50} > 11 ppm. However, RAC notes that among the studies considered acceptable, a rather steep dose response for mortality is apparent. In Nachreiner and Dodd (1986) with an LC_{50} of 57 ppm, 30% animals died at 55 ppm while 90% mortality was achieved at 64 ppm. In Newton (1991), no animals died at concentrations up to 18 ppm and 50% of the animals died at 28 ppm. In the mouse study, no animals died at concentrations up to 26.5 ppm, while 100% mortality was reported at 33.4 ppm. Considering the steep dose-response curve, the study by Newton (1993) with no mortalities up to the highest tested dose of 11 ppm is of limited value for the derivation of the ATE value.

Taking into account deficiencies in all available studies and the steep dose-response curve demonstrated in most of these studies, RAC decides to take a conservative approach using the converted acute toxicity point estimate from CLP Annex I, Table 3.1.2 for the derivation of the ATE value. The default ATE value of 10 ppmV for gases in category 1 is supported by the available database giving the 4-hour LC_{50} values in the range of 11-57 ppm. **RAC concludes that an ATE value of 10 ppmV is warranted for acute inhalation toxicity of phosphine.**

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).