Committee for Risk Assessment

RAC

Annex 1

Background document

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

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

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

30 November 2018

CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2

International Chemical Identification:

Phosphine

EC Number: 232-260-8

CAS Number: 7803-51-2

Index Number: 015-181-00-1

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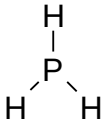
CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	Phosphine Phosphine gas
Other names (usual name, trade name, abbreviation)	Phosphine, hydrogen phosphide, Phosphorus (tri)hydride Phosphorus(III)hydride Monophosphane Phosphane CYTOP 1
ISO common name (if available and appropriate)	There is no ISO common name.
EC number (if available and appropriate)	232-260-8
EC name (if available and appropriate)	Phosphine
CAS number (if available)	7803-51-2
Other identity code (if available)	127
Molecular formula	H_3P
Structural formula	
SMILES notation (if available)	
Molecular weight or molecular weight range	34 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	/
Description of the manufacturing process and identity of the source (for UVCB substances only)	/
Degree of purity (%) (if relevant for the entry in Annex VI)	The minimum purity is 994 g/kg.

Note: several names exist for the active substance. The EC name is phosphine and has been used for the redaction of the CLH report.

Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)
Phosphine	99.4	Press Gas, Flam Gas 1 H220, Skin Corr 1B H314 Acute Tox 2* H330 Aquatic acute 1 H400	Existing harmonized classification

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
Arsine	0.0023	Press Gas Flam Gas 1 H220 Acute Tox 2* H330 STOT RE 2* H373** Aquatic acute 1 H400 Aquatic Chronic H410	Existing harmonized classification	No

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 4:

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	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	Press. Gas Flam. Gas 1 Skin Corr. 1B Acute Tox. 2* Aquatic Acute 1	H220 H314 H330 H400	Danger GHS02 GHS09 GHS05 GHS06 GHS04	H220 H314 H330 H400	-	-	U
Dossier submitters proposal	015-181-00-1	Phosphine	232-260-8	7803-51-2	Acute Tox. 1	H330	GHS06	H330	-	-	-
Resulting Annex VI entry if agreed by RAC and COM	015-181-00-1	Phosphine	232-260-8	7803-51-2	Press. Gas Flam. Gas 1 Skin Corr. 1B Acute Tox. 1 Aquatic Acute 1	H220 H314 H330 H400	Danger GHS02 GHS09 GHS05 GHS06 GHS04	H220 H314 H330 H400	-	-	U

Table 5: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	Hazard class not applicable	No
Flammable gases (including chemically unstable gases)	Hazard class not assessed in this dossier Current harmonized classification: Flam Gas 1 H220	No
Oxidising gases	Hazard class not assessed in this dossier	No
Gases under pressure	Current harmonized classification: Press Gas	No
Flammable liquids	Hazard class not applicable	No
Flammable solids	Hazard class not applicable	No
Self-reactive substances	Hazard class not assessed in this dossier	No
Pyrophoric liquids	Hazard class not applicable	No
Pyrophoric solids	Hazard class not applicable	No
Self-heating substances	Hazard class not applicable	No
Substances which in contact with water emit flammable gases	Hazard class not applicable	No
Oxidising liquids	Hazard class not applicable	No
Oxidising solids	Hazard class not applicable	No
Organic peroxides	Hazard class not applicable	No
Corrosive to metals	Hazard class not assessed in this dossier	No
Acute toxicity via oral route	Hazard class not assessed in this dossier	No
Acute toxicity via dermal route	Hazard class not assessed in this dossier	No
Acute toxicity via inhalation route	Proposed harmonised classification : Acute Tox. 1 – H330	Yes
Skin corrosion/irritation	Current harmonized classification: Skin Corr. 1B – H314	No
Serious eye damage/eye irritation	Hazard class not assessed in this dossier	No
Respiratory sensitisation	Hazard class not assessed in this dossier	No
Skin sensitisation	Hazard class not assessed in this dossier	No
Germ cell mutagenicity	Hazard class not assessed in this dossier	No
Carcinogenicity	Hazard class not assessed in this dossier	No
Reproductive toxicity	Hazard class not assessed in this dossier	No
Specific target organ toxicity-single exposure	Hazard class not assessed in this dossier	No
Specific target organ toxicity-repeated exposure	Hazard class not assessed in this dossier	No
Aspiration hazard	Hazard class not assessed in this dossier	No
Hazardous to the aquatic environment	Hazard class not assessed in this dossier Current harmonized classification: Aquatic acute 1 – H400	No
Hazardous to the ozone layer	Hazard class not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

Phosphine has an harmonized classified according to the Directive 67/548/EEC: F+; R12, R17, T+; R26, C; R34, N; R50.

This classification was translated into CLP regulation (CLP00): Press. Gas; Flam. Gas 1 – H220; Skin Corr. 1B - H314; Acute Tox. 2* - H330; Aquatic Acute 1 – H400.

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).

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Because the classification according to the criteria in Directive 67/548/EEC does not correspond directly to the classification in a hazard class and category under CLP regulation, a minimal classification is currently available for acute toxicity by inhalation for phosphine.

France would like to progressively suppress all the minimal classifications in order to improve the risk management of these substances. The need to update the classification of phosphine regarding its acute toxicity by inhalation is justified considering the wide use of this substance in fumigation activities, with the

occurrence of cases of (sub)fatal accidents. In addition, concerning fumigated products, there is a national and European plan for a better occupational risk control for workers manipulating those products.

5 IDENTIFIED USES

This substance is used as an insecticide under PPP (phytopharmaceutical products) Regulation.

Other following uses are reported in ECHA website:

- This substance is used in the following products: semiconductors.
- This substance is used for the manufacture of: electrical, electronic and optical equipment.

6 DATA SOURCES

This CLH dossier is based on the available data on the REACH registration dossier of phosphine, but also on the RAC opinions on aluminium phosphide and trimagnesium disphosphide (2011a, b) and on the DAR on phosphine (2010).

7 PHYSICOCHEMICAL PROPERTIES

Data reported below comes from the DAR on phosphine (2010).

Table 6: Summary of physicochemical properties

Property	**Value**	**Reference**	**Comment (e.g. measured or estimated)**
Physical state at 20°C and 101,3 kPa	Gas Colourless Pure phosphine is odourless. Phosphine technical has a fishy or garlicky odour.	Lewis, 2000 (report BVL no 1693122) Anonymous, 1989 (report BVL no 1693123)	Method and material tested not reported
Melting/freezing point	-133.8 °C	Lide, 2004 (report BVL no 1693118)	Chemical textbook
Boiling point	-87.75 °C	Lide, 2004 (report BVL no 1693119)	Chemical textbook
Relative density	1.390 g/L (~ 10^5 Pa)	Lide, 2004 (report BVL no 1693120)	Chemical textbook
Vapour pressure	At -144.48 °C the vapour pressure was found to be 1063.91 Pa.	Gmelin, 1965 (report BVL no 1693121)	Chemical textbook
Surface tension	Not applicable. Based of its chemical nature no influence of the surface tension is expected.		
Water solubility	371 mg/L (260 cm^3 in 1000 cm^3	Gmelin [original founder], 1965	Chemical textbook

Property	Value	Reference	Comment (e.g. measured or estimated)
	water at 17 °C).	(report BVL no 1693133)	
Partition coefficient n-octanol/water	log P_{OW}: -0.27 Investigations concerning the possible pH dependency are not applicable.	Tiemann, 2006 (report BVL no 1693136)	Calculation KOWWIN (Version 1.66)
Flash point	Not applicable		
Flammability	Phosphine is extremely flammable. Classified as F^+ under Directive 67/548/EEC. Harmonised classification under CLP regulation: Flam Gas 1 H220 (worst case).	Anonymous, 1989 (WHO report) (report BVL no 1693138)	Method not reported Material tested not reported Not GLP
Explosive properties	Not applicable in the sense of EEC A14. Phosphine forms explosive mixtures with air at concentrations greater than 1.8 %.	Anonymous, 1989 (WHO report) (report BVL no 1693140)	Method not reported Material tested not reported Not GLP
Self-ignition temperature	The auto-ignition temperature of pure phosphine is 38 °C. Technical phosphine technical ignites spontaneously in air at ambient temperatures at concentrations above 1.8 %. Classified as R17 under Directive 67/548/EEC (spontaneously flammable in air). Harmonised classification under CLP regulation : Flam Gas 1 H220 covers this point.	Anonymous, 1989 (WHO report) (report BVL no 1693139)	Method not reported Material tested not reported Not GLP
Oxidising properties	Not applicable in the sense of EEC A17. No EC or OECD test guideline for the oxidative properties of gas is available, but phosphine must be stated to be corrosive to metals,	Document M-II (report BVL no 1693222) and Anonymous, 1989 (WHO report) (report BVL no 1693141)	Method not reported Material tested not reported Not GLP Not acceptable. This information does not address the issue of the Annex point.

Property	Value	Reference	Comment (e.g. measured or estimated)
	particularly to copper and copper alloys. Due to the low redox potential of phosphane in acidic solutions (-0.063 V) and in alkaline solutions (-0.891 V) phosphine is a reducing agent without any oxidising properties. At 150 °C phosphine will be oxidised to phosphoric acid only in the presence of oxygen acting as a reducing agent.		
Granulometry	Not applicable		
Stability in organic solvents and identity of relevant degradation products	The solubility of phosphine in organic solvents was found to be: Ethanol: 695 mg/L Ether: 2.78 g/L Spirits of turpentine: 4.52 g/L (all at 18 °C) Cyclohexanol: 3.97 g/L (all at 26 °C)	Gmelin [original founder], 1965 (report BVL no 1693135)	Method not reported Material tested not reported Not GLP
Dissociation constant	Not applicable. It is known from chemical textbooks that the pK_b of phosphine is in the order of 26. Also its acid properties can only be revealed with extreme bases.	No reference	Chemical textbook
Viscosity	Not applicable		

8 EVALUATION OF PHYSICAL HAZARDS

Current harmonised classification: Press Gas, Flam Gas 1 - H220. Hazard physical classes were not re-assessed.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Table 7: Summary table of toxicokinetic studies

Method	Results	Remarks	Reference

Method	Results	Remarks	Reference
Inhalation	Inhaled phosphine (PH_3) is considered to be readily absorbed through the lungs and Excreted with urine as hypophosphite and phosphite and via lungs as PH_3		WHO (1988) (TOX2005-1201)

9.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

Few data are available on the toxicokinetics of phosphine. The information below are based on the WHO/IPCS report (1988).

Phosphine is generally considered to be readily absorbed through the lungs. Inhaled phosphine produces neurological and hepatic symptoms suggesting that it reaches the nervous system and liver. Ingested phosphides have been shown to reach the liver and blood in rats and human beings. In rats, phosphine that is not excreted in the expired air is oxidized and appears in the urine, mainly as hypophosphite and phosphite. An unidentified metabolite is also reported, detectable by paper chromatography and distinct from pyrophosphate and metaphosphate. The fact that phosphine is incompletely oxidized and the proportion of an administered dose that is eliminated as expired phosphine increases with the dose suggests that the oxidative pathway is slow.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

10.1 Acute toxicity - oral route

Hazard class not evaluated in this dossier

10.2 Acute toxicity - dermal route

Hazard class not evaluated in this dossier

10.3 Acute toxicity - inhalation route

Table 8: Summary table of animal studies on acute inhalation toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, form and particle size (MMAD)	Dose levels, duration of exposure	Value LC_{50}	Reference
Acute inhalation toxicity study, US EPA, whole body. GLP Acceptable	Rat SD, 5M + 5F/group	PH_3	9-19-22-35-55-64-109 ppm 4 h	LC_{50}: 57 ppm (M/F) (0.08 mg/L)	Nachreiner, D.J. and Dodd, D.E. (1986)
Acute inhalation toxicity study, US EPA, head only. GLP. Acceptable	Rat SD Part 1: 5M+5F/group Part 2: 10M/group	1% PH_3 in nitrogen	Part 1: 0-1.3-6-28 ppm Part 2: 3.1-10-18 6 h	No LC_{50} was calculated, 50% mortality at 28 ppm	Newton, P.E. (1991)
Acute inhalation toxicity study. No guideline, non	Rat Wistar, 5M + 5F/group	PH_3, developed from magnesium phosphide	0 - 15.4 – 26 - 47 ppm 4h	LC_{50}: 34.6 ppm (0.048 mg/L)	Roy, B.C. (1998)

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance, form and particle size (MMAD)**	**Dose levels, duration of exposure**	**Value** LC_{50}	**Reference**
GLP Acceptable					
Acute inhalation toxicity study whole body, US EPA. GLP. Acceptable	Rat Fisher 344 15/sex/group	PH_3	2.4 - 4.9 - 11 ppm 6 h	LC_{50}: > 11 ppm (M/F) (> 0.016 mg/L or > 0.675 mg/kg bw)	Newton, P.E. (1993)
Acute inhalation toxicity study, whole body, exposure Similar to OECD 403, Non-GLP Not reliable	Rat, Slc:SD 10M + 10F/group	PH_3, developed from magnesium phosphide	150 – 165 – 182 – 200 – 220 – 242 ppm 1 h	LC_{50}: 204/179 ppm (M/F) (0.29/0.25 mg/L air (M/F) or 12.9/11.4 mg/kg bw (M/F))	Shimizu, Y. *et al.* (1982)
Acute inhalation toxicity study, whole body, Similar to OECD 403, Non-GLP Acceptable	Rat ChR-CD 6M/group	PH_3 (gaseous phosphine)	Dose levels not reported 4 hours	LC_{50} M: 11 ppm equivalent to: 0.015 mg PH_3 /L air	Waritz, R.S. and Brown R.M. (1975); Amer. Ind. Hyg. Assoc. J., p 452
Acute inhalation toxicity study Equivalent or similar to Guideline: OECD Guideline 403, GLP not specified Acceptable	Mouse ICR 10M/group	99.995% pure PH_3	First experiment: 17.2 ppm ; 25.1 ppm ; 31.7 ppm ; 41.6 ppm ; 59.2 ppm for 1 hour Second experiment: 22.5 ppm ; 26.5 ppm ; 33.4 ppm ; 45.5 ppm ; 66.9 for 4 hours	LC_{50} for 1 hour exposure was greater than 59.2 ppm and that for 4-hour exposure was between 26.5 ppm and 33.4 ppm.	Omae K., Ishizuka C. and Nakashima H 1996
Acute inhalation toxicity study Non-guideline, Non-GLP Not reliable	Rat Wistar female 6/dose	PH_3, developed from aluminium phosphide	Sample A : 20 ppm for 6 h ; 40 ppm for 4 h ; 27 ppm for 8 h ; 40 ppm for 6 h. Sample B : 33 ppm for 6 h ; 60 ppm for 4 h ; 33 ppm for 8 h.	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 products A and B.	Muthu M., Krishnakumari M.K., Muralidhara V. and Majumder S.K. 1980

M: male
F: female

10.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

Phosphine is currently classified as T+; R26 "Very toxic by inhalation" according to Directive 67/548/EC and translated into a minimum classification as Acute Tox. 2* (inhalation) H330: "Fatal if inhaled" according to the CLP Regulation.

It has to be noted that RAC opinions on the harmonised classification and labelling for acute inhalation toxicity of aluminium phosphide and trimagnesium diphosphide are available (ECHA, 2011a, b) with three studies in common with the current dossier : Waritz, R.S. and Brown R.M. (1975), Roy, B.C.(1998), and Shimizu, Y. *et al.* (1982). Aluminium phosphide and trimagnesium disphosphide readily release phosphine by hydrolysis, which is responsible for most of the toxic activity of metal phosphides. The committee concluded that the highest values **204/179 ppm** (male/female) were obtained from the study (Shimizu, 1982) where exposure lasted only for 1 hour and concentration was not measured but calculated based on amount of Mg_3P_2 added to a chamber with water. The LC_{50} value of **34.6 ppm** was obtained based on the study of Roy (1998), where the method of measurement is not very well documented. Due to deficiencies reported in Roy, (1998), it was proposed to take the LC_{50} value obtained from the Waritz and Brown study (1975): **11 ppm**.

Among other studies identified, 3 were published.

In the study of Newton *et al.* (1993), 15 Fischer rats/sex were exposed for 6 hours to 0, 2.4, 4.9 and 11 ppm (analytical exposure). All animals survived these exposures, consequently **no LC_{50}** can be derived. This study was assessed in the DAR and considered supplementary. Beyond the fact that the exposures last 6 hours (instead of 4 hours as stated in guidelines), the authors have maybe selected too low concentrations.

The study by Muthu *et al.* (1980) has an unusual protocol. Six Wistar rats per dose were exposed to different samples of the substance (A or B, without any details on these samples), and at different exposure times (4 to 8 hours). From these exposures, the authors derived concentration-time products. For the sample A, the LC_{50} derived was **28 ppm for 5.2 hours** of exposure, and for the sample B, **33.3 ppm for 7.4 hours** of exposure. With regard to the protocol and the missing information, the results of this study seem difficult to interpret.

In the study by Omae *et al.* (1996), ICR male mice (10/group) were exposed for 4 hours to 22.5, 26.5, 33.4, 45.5 and 66.9 ppm. No mortality was noted at the two lowest concentrations (22.5 and 26.5 ppm), and all animals died at the three others concentrations (33.4, 45.5 and 66.9 ppm). The authors concluded that the LC_{50} was **between 26.5 and 33.4 ppm**. It has to be noted that, in the other experiment lasting 1 hour, the authors did not observed mortality up to 59.2 ppm.

Finally, two other studies identified were not published, but summarised in the DAR (2010).

The study from Nachreiner *et al.* (1986) has been assessed in the draft assessment report (DAR) (2010) of phosphine and was considered acceptable. Sprague Dawley rats (5/sex/group) were exposed by inhalation route for 4 hours at actual concentrations of 9, 19, 22, 35, 55, 64 and 109 ppm. The study was conducted according the OPPTS guideline and GLP. No mortality was noted at the four lowest concentrations (9, 19, 22 and 35 ppm), 3/10 animals died at 55 ppm, 9/10 at 64 ppm, and all animals died at 109 ppm. The authors concluded that the four-hour inhalation LC_{50} in rats of phosphine was approximately **57 (49-66) ppm** for the combined sexes.

The study from Newton *et al.* (1991) has also been assessed in the DAR. Sprague Dawley rats (5/sex) were exposed for 6 hours to 0, 1.3, 6, and 28 ppm. **No LC_{50}** was calculated, but a 50 % mortality of animals was observed at an actual concentration of 28 ppm phosphine. It was considered as supplementary data: unless it was conducted according to OPPTS guidelines and under GLP, there were some deviations (exposure period was 6 hours, no necropsy data submitted, and no LC_{50} calculated...).

10.3.2 Comparison with the CLP criteria

Overall, on the eight studies available :

- 5 derived LC_{50} that fall into category 1 (< 100 ppm);

- 2 were not able to derive LC_{50};
- 1 derived LC_{50} that fall into category 2 (100-500 ppm)

Based on a weight of evidence, except the study of Shimizu *et al.* (1982), all studies allowing the derivation of a LC_{50} fall into category 1 criteria for acute inhalation toxicity (< 100 ppm). The study from Shimizu *et al.* (1982) suffer from serious deficiencies : exposure lasted only for 1 hour and concentration was not measured but calculated based on amount Mg_3P_2 added to a chamber with water. For information, LC_{50} from this study for 4 hours calculated with the Haber's law would have been 51/45 (male/female) ppm, which is consistent with results of other studies and therefore with criteria for a classification as Acute Tox.1. Concerning the studies that were not able to derive a LC_{50}, for one of them, concentrations selected may be too low (Newton *et al.*, 1993). For the other one, the LC_{50}, even if not derived by the authors, could be 28 ppm as half of the animals died at this concentration (Newton *et al.*, 1991). Results are therefore relatively consistent between studies.

It has to be noted that, neither the toxicokinetics data (showing a systemic activity) nor the physical and chemical properties available suggest a corrosive action of phosphine.

According to CLP guidance document (2015), in general, classification is based on the lowest LC_{50} value available. Consequently, classification in category 1 (gases) – H330 is warranted as the majority of studies derives an LC_{50} clearly under 100 ppm, the upper limit of the category.

It can be noted that in the report for aluminium phosphide, RAC provided additional recommendations for phosphine classification : "*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. While the classification according to the DSD Directive, T+; R26, is appropriate since all LC_{50} values are in a range of 0.015 – 0.072mg/l which is well below the DSD guidance value ≤0.5mg/l/4h for this category*", which are therefore in line with our conclusions.

For the classification of mixtures containing phosphine, FR is of the opinion to retain the acute toxicity estimate (ATE) value of 11 ppm, *i.e.* the LC_{50} from the study of Waritz *et al*. Despite the lack of information in the study (doses used and mortality not given), this is the lowest LC_{50} available. Moreover, considering the uncertainties of the database (general quality of the studies), FR made the choice to select the most conservative value.

10.3.3 Conclusion on classification and labelling for acute inhalation toxicity

Phosphine should be classified in acute hazard category 1 for inhalation, H330, according to the Regulation (EC) 1272/2008/EC.

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-	PH_3 generated from Mg_3P_2	150-165-182-200-242 ppm	No mortality at 150 ppm; 3/10 (F) and 0/10 (M) died at 165 ppm; 6/10 (F) and 1/10	Shimizu, Y., Ogawa, Y. and

Dawley, 10/sex /dose, whole body 14 days recovery period **Not reliable** (no data for concentration measurement)		1h 4h (calculated with Haber´s law)	(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	Tokiwa, K. (1982)
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 for phosphine.**

10.4 Skin corrosion/irritation

Hazard class not evaluated in this dossier

10.5 Serious eye damage/eye irritation

Hazard class not evaluated in this dossier

10.6 Respiratory sensitisation

Hazard class not evaluated in this dossier

10.7 Skin sensitisation

Hazard class not evaluated in this dossier

10.8 Germ cell mutagenicity

Hazard class not evaluated in this dossier

10.9 Carcinogenicity

Hazard class not evaluated in this dossier

10.10 Reproductive toxicity

Hazard class not evaluated in this dossier

10.11 Specific target organ toxicity-single exposure

Hazard class not evaluated in this dossier

10.12 Specific target organ toxicity-repeated exposure

Hazard class not evaluated in this dossier

10.13 Aspiration hazard

Hazard class not evaluated in this dossier

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Hazard class not evaluated in this dossier

12 EVALUATION OF ADDITIONAL HAZARDS

Hazard class not evaluated in this dossier

13 ADDITIONAL LABELLING

14 REFERENCES

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15 ANNEXES

Separate Annex I and confidential annex to the CLH report .