Committee for Risk Assessment

RAC

Annex 1

Background document

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

tricalcium diphosphide

EC number: 215-142-0

CAS number: 1305-99-3

ECHA/RAC/CLH-O-0000003602-81-01/A1

Adopted
7 March 2013

CLH report

Proposal for Harmonised Classification and Labelling

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

Substance Name: Tricalcium Diphosphide

EC Number: **215-142-0**

CAS Number: **1305-99-3**

Index Number: **015-003-00-2**

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Version number: **2.0 (post ACCheck)**

Date: **May 2012**

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Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	***Tricalcium Diphosphide***
EC number:	***215-142-0***
CAS number:	***1305-99-3***
Annex VI Index number:	***015-003-00-2***
Degree of purity:	***min. 180 g/kg***
Impurities:	***no relevant impurities***

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	Regulation (EC) No 1272/2008 (2nd ATP)	Directive 67/548/EEC (Dangerous Substances Directive; DSD)
Current entry in Annex VI, CLP Regulation	Water-react. 1; H260 Acute Tox. 2*; H300 Aquatic Acute 1; H400 M-factor = 100	F; R15 T^+; R28 R29 N; R50 Concentration Classification C ≥ 0.25% N; R50 where C is the concentration of tricalcium diphosphide in the preparation
Current proposal for consideration by RAC	Acute Tox. 2; H300 Acute Tox. 3; H311 Skin Corr. 1A; H314	R28 Xn; R21 C; R35
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Water-react. 1; H260 Acute Tox. 2; H300 Acute Tox. 3; H311 Skin Corr. 1A; H314	F; R15 T^+; R28 Xn; R21 C; R35

	Aquatic Acute 1; H400 M-factor = 100	R29 N; R50 Concentration Classification C ≥ 0.25% N; R50 where C is the concentration of tricalcium diphosphide in the preparation

1.3 Proposed harmonised classification and labelling based on CLP Regulation and/or DSD criteria

Proposed harmonised classification and labelling is summarized in tables 3-6.

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives				Conclusive but not sufficient for classification
2.2.	Flammable gases				
	Contact with water liberates toxic gas	EUH029		EUH029	
2.3.	Flammable aerosols				
2.4.	Oxidising gases				
2.5.	Gases under pressure				
2.6.	Flammable liquids				
2.7.	Flammable solids				
2.8.	Self-reactive substances and mixtures				
2.9.	Pyrophoric liquids				
2.10.	Pyrophoric solids				
2.11.	Self-heating substances and mixtures				
2.12.	Substances and mixtures which in contact with water emit flammable gases	Water-react. 1; H260		Water-react. 1; H260	
2.13.	Oxidising liquids				
2.14.	Oxidising solids				Conclusive but not sufficient for classification
2.15.	Organic peroxides				
2.16.	Substance and mixtures corrosive to metals				
3.1.	Acute toxicity - oral	Acute Tox. 2; H300		Acute Tox. 2*; H300	
	Acute toxicity - dermal	Acute Tox. 3; H311		None	
	Acute toxicity – inhalation	none		none	Data lacking
3.2.	Skin corrosion / irritation	Skin Corr. 1A; H314		none	
3.3.	Serious eye damage / eye irritation	Risk of severe eye damage is considered implicit		none	
3.4.	Respiratory sensitisation	none		none	Data lacking
3.4.	Skin sensitisation	none		none	Conclusive but not sufficient for classification

3.5.	Germ cell mutagenicity	none		none	Conclusive but not sufficient for classification
3.6.	Carcinogenicity	none		none	Conclusive but not sufficient for classification
3.7.	Reproductive toxicity	none		none	Conclusive but not sufficient for classification
3.8.	Specific target organ toxicity –single exposure	none		none	Conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure	none		none	Conclusive but not sufficient for classification
3.10.	Aspiration hazard	none		none	
4.1.	Hazardous to the aquatic environment	Aquatic Acute 1; H400	M-factor: 100	Aquatic Acute 1; H400 M-factor: 100	
5.1.	Hazardous to the ozone layer				

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Table 4: Proposed labelling based according to the CLP Regulation

	Labelling	Wording
Pictograms	GHS02 GHS05 GHS06 GHS09	
Signal Word	Danger	
Hazard statements	H260 H300 H311 H314 H400	In contact with water releases flammable gases which may ignite spontaneously Fatal if swallowed Toxic in contact with skin Causes severe skin burns and eye damage Very toxic to aquatic life
Suppl. Hazard statements	EUH029	Contact with water liberates toxic gas
Precautionary statements	(P102) P223 P231 + P232 P234 P260 P273 P280 P301 + P330 + P331 P305 + P351 + P338 P310 P321 P335 P370 + P378 P402 + P404 P405 P501	(Keep out of reach of children) Keep away from any possible contact with water, because of violent reaction and possible flash fire Handle under inert gas. Protect from moisture Keep only in original container Do not breathe dust Avoid release to the environment Wear protective gloves/ protective clothing/ eye protection/ face protection IF SWALLOWED: rinse mouth. Do NOT induce vomiting. IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Immediately call a POISON CENTER or doctor/ physician. Specific treatment (see … on this label) Brush off loose particles from skin In case of fire: Use … for extinction Store in a dry place. Store in a closed container Store locked up Dispose of contents/container to …

Proposed notes assigned to an entry:

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Table 5: Proposed classification according to DSD

Hazardous property	Proposed classification	Proposed SCLs	Current classification [1)]	Reason for no classification [2)]
Explosiveness				Conclusive but not sufficient for classification
Oxidising properties				Conclusive but not sufficient for classification
Flammability	F; R15		F; R15	
Thermal stability				
Acute toxicity	T^+; R28 Xn; R21 R29		T^+; R28 R29	
Acute toxicity – irreversible damage after single exposure	none		none	Conclusive but not sufficient for classification
Repeated dose toxicity	none		none	Conclusive but not sufficient for classification
Irritation / Corrosion	C; R35		none	
Sensitisation	none		none	Conclusive but not sufficient for classification
Carcinogenicity	none		none	Conclusive but not sufficient for classification
Mutagenicity – Genetic toxicity	none		none	Conclusive but not sufficient for classification
Toxicity to reproduction – fertility	none		none	Conclusive but not sufficient for classification
Toxicity to reproduction – development	none		none	Conclusive but not sufficient for classification
Toxicity to reproduction – breastfed babies. Effects on or via lactation	none		none	Data lacking
Environment	N; R50	$C \geq 0.25$ % [3)] classification of preparation is N; R50	N; R50 $C \geq 0.25$ % [3)] classification of preparation is N; R50	

[1)] Including SCLs
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification
[3)] C is the concentration of tricalcium diphosphide in the preparation

Table 6: Proposed labelling according to DSD

	Labelling	Wording
Hazard Symbols, Indications of danger	F T^+ C N	Highly flammable Very toxic Corrosive Dangerous to the environment
R-phrases	R15/29 R21 R28 R35 R50	Contact with water liberates toxic extremely flammable gas Harmful in contact with skin Very toxic if swallowed Causes severe burns Very toxic to aquatic organisms
S-phrases	S(1/2) S3/9/14/49 S8 S22 S26 S30 S36/37/39 S43 S45 S60 S61	Keep locked up and out of the reach of children Keep only in the original container in a cool, well-ventilated place away from ... (incompatible materials to be indicated by the manufacturer) Keep container dry Do not breathe dust In case of contact with eyes, rinse immediately with plenty of water and seek medical advice Never add water to this product Wear suitable protective clothing, gloves and eye/face protection In case of fire use … Never use water In case of accident or if you feel unwell, seek medical advice immediately. (Show the label where possible.) This material and/or its container must be disposed of as hazardous waste Avoid release to the environment. Refer to special instructions/ Safety data sheet

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

2.2 Short summary of the scientific justification for the CLH proposal

No acute oral toxicity study for calcium phosphide has been submitted by the applicant and no justification was given for that. However, there exist respective studies with other phosphides. Metal phosphides in contact with moisture (GI tract) readily decompose to metal or calcium hydroxide and phosphine, the toxicological principle. Due to the decomposition by moisture other phosphides are regarded as adequate model compounds. Studies with aluminium phosphide and magnesium phosphide are available and are considered to be of high toxicity when administered orally to animals. Therefore calcium phosphide has to be classified as 'Fatal if swallowed' (Acute Tox.2; H300) and 'Very toxic if swallowed' (T+; R28) resp.

No acute inhalation study on calcium phosphide is available. However, in contact with water calcium phosphide liberates a toxic gas and therefore the Suppl. Hazard statement Code (EUH029) is appropriate. PH_3 itself is classified as 'Fatal if inhaled' (Acute Tox. 2; H330) and 'Very toxic by inhalation' (T+; R26) resp., but metal phosphides are not classified with regard to inhalation toxicity.

No dermal toxicity study on calcium phosphide has been submitted but on aluminium phosphide. Regarding calcium phosphide no higher acute dermal toxicity than observed in aluminium phosphide e.g. is expected (LD_{50} 460 – 900 mg/kg bw). Therefore, classification as 'Toxic in contact with skin' (Acute Tox. 3; H311) and 'Harmful in contact with skin' (Xn; R21) resp., is required.

Neither skin nor eye irritation study for calcium phosphide has been submitted. However, based on the irritant properties of calcium hydroxide (hydrolysis product of calcium phosphide) calcium phosphide should be considered as a corrosive substance and classified accordingly (Skin Corr. 1A; H314/C; R35).

Calcium phosphide is a dry granular solid which decomposes very rapidly in contact with water to produce calcium hydroxide and phosphine gas. For aquatic toxicity no data are available for calcium phosphide, but data for Phosphine (PH_3) from studies with Aluminium phosphide is available, which can be used. The acute toxicity of Calcium phosphide was recalculated from studies with Aluminium Phosphide. The mortality to rainbow trout (*Oncorhynchus mykiss)* for Phosphine was determined in a 96 hr static test. The recalculated LC_{50} for Ca_3P_2 is 12.5 µg/L (nominal). This data is relevant for determination of M-factor of 100.

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

Table 7: Current classification in Annex VI, Table 3.1 in the CLP Regulation

Index number: 015-003-00-2	Classification	Wording
Hazard classes, Hazard categories	Water-react. 1 Acute Tox. 2* Aquatic Acute 1	
Hazard statements	H260 H300 H400	In contact with water releases flammable gases which may ignite spontaneously Fatal if swallowed Very toxic to aquatic life

Table 8: Current labelling in Annex VI, Table 3.1 in the CLP Regulation

Index number: 015-003-00-2	Labelling	Wording
Pictograms	GHS02 GHS06 GHS09	
Signal Word	Danger	
Hazard statements	H260 H300 H400	In contact with water releases flammable gases which may ignite spontaneously Fatal if swallowed Very toxic to aquatic life
Suppl. Hazard statements	EUH029	Contact with water liberates toxic gas
Precautionary statements	-	-

2.3.2 Current classification and labelling in Annex VI, Table 3.2 in the CLP Regulation

Table 9: Current classification in Annex VI, Table 3.2 in the CLP Regulation

Index number: 015-003-00-2	Classification	Wording
Hazard Symbols, Indications of danger	F T^+ N	Highly flammable Very toxic Dangerous for the environment
R-phrases	R15 R28 R29 R50	Contact with water liberates extremely flammable gases Very toxic if swallowed Contact with water liberates toxic gas Very toxic to aquatic organisms

Table 10: Current labelling in Annex VI, Table 3.2 in the CLP Regulation

Index number: 015-003-00-2	Labelling	Wording
Hazard Symbols, Indications of danger	F T^+ N	Highly flammable Very toxic Dangerous to the environment
R-phrases	R15/29 R28 R50	Contact with water liberates toxic extremely flammable gas Very toxic if swallowed Very toxic to aquatic organisms
S-phrases	S(1/2) S22 S28 S36/37 S43 S45 S61	Keep locked up and out of the reach of children Do not breathe dust After contact with skin, wash immediately with plenty of ... (to be specified by the manufacturer) Wear suitable protective clothing and gloves In case of fire use … Never use water In case of accident or if you feel unwell, seek medical advice immediately. (Show the label where possible.) Avoid release to the environment. Refer to special instructions/ Safety data sheet

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Tricalcium Diphosphide is an active substance in the meaning of Directive 91/414/EEC.

In accordance with Article 36(2) of the CLP Regulation, Tricalcium Diphosphide should now be considered for harmonized classification and labelling.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

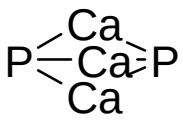
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 11: Substance identity

EC number:	215-142-0
EC name:	Calcium phosphide
CAS number (EC inventory):	
CAS number:	1305-99-3
CAS name:	Calcium phosphide
IUPAC name:	Calcium phosphide
CLP Annex VI Index number:	015-003-00-2
Molecular formula:	Ca_3P_2
Molecular weight range:	182.19

Structural formula:



1.2 Composition of the substance

Table 12: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Calcium phosphide	> 180 g/kg		

Current Annex VI entry: 015-003-00-2

For the content of impurities see confidential annex to CLH report.

1.2.1 Composition of test material

1.3 Physico-chemical properties

Table 13: Summary of physico - chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
State of the substance at 20°C and 101,3 kPa	solid granules	Monograph Assessment Report EFSA conclusions	
Melting/freezing point	approx. 1600 °C		
Boiling point	not relevant		
Relative density	1.274		
Vapour pressure	< $1x10^{-3}$ Pa		
Surface tension	not applicable		
Water solubility	not applicable, reaction with water		
Partition coefficient n-octanol/water	not applicable, reaction with water		
Flash point	not applicable		
Flammability	not flammable, but liberates extremely flammable gas in contact with water		
Explosive properties	not explosive, based on structure		
Self-ignition temperature	no self-ignition up to 404 °C		
Oxidising properties	not oxidising, based on structure		
Granulometry	n.d.		no data requirement for active substances according to directive 91/414/EC For a product the following values were determined: 16.3 % of particles > 10 mm, 10.1 % of particles < 1 mm.
Stability in organic solvents and identity of relevant degradation products	n.d.		no data requirement for active substances according to directive 91/414/EC
Dissociation constant	n.d.		
Viscosity	n.d.		no data requirement for active substances according to directive 91/414/EC

2 IDENTIFIED USES

Calcium phosphide is a rodenticidal active substance to control rodents and moles (and other non-rodent vertebrates) in the field (cropland and non-cropland situations).

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Not relevant for this dossier. There is no need for an amendment of the current classification.

RAC general comment

Tricalcium diphosphide belongs to a group of metal phosphides together with aluminium phosphide, trimagnesium diphosphide and trizinc diphosphide; these four substances fulfil the criteria for grouping and read across, as defined in section 1.5 of Annex XI of the Regulation 1907/2006/EC, because they have the following common characteristics:

1) they have a common functional group, which in this case is the phosphorus atom, which during breakdown of metal phosphide release a phosphorus radical with trivalent binding capability;

2) all the metal phosphides have common breakdown products via physical-chemical process, particularly as a result of hydrolysis of phosphides in contact with water or biological fluids which is phosphine (PH_3). This substance is in fact responsible for most of the toxicity of metal phosphides.

Since the two criteria for this grouping and read across approach (common functional group and common breakdown product) are fulfilled it is highly probable that their physicochemical, toxicological and ecotoxicological properties are similar. Therefore, in the assessment of hazardous properties of tricalcium diphosphide the results of studies performed on other metal phosphides were also used.

When converting the doses of the other metal phosphides or PH_3 into tricalcium diphosphide it has to be considered that they all release different maximum amounts of phosphine (due to different mass fraction of phosphorus in the respective compounds). This information is summarized in table 1 below.

Table 1: Conversion of metal phosphides to % phosphorus and amounts of phosphine

Metal phosphide	**Molecular formula**	**Molecular weight [g/mol]**	**Phosphorus [%]**	**Max. amount of PH_3 [g PH_3/g metal phosphide]**	**1 g metal phosphide equiv. to x g tricalcium diphosphide**
Tricalcium diphosphide	Ca_3P_2	182.19	34.0	0.37	1
Aluminium phosphide	AlP	57.95	53.4	0.59	1.59
Magnesium phosphide	Mg_3P_2	134.86	45.9	0.50	1.35
Zinc phosphide	Zn_3P_2	258.09	24.0	0.26	0.70

The phosphine (PH_3), which develops after contact of tricalcium diphosphide with water by spontaneous hydrolysis of the phosphide, is a very toxic gas. PH_3 is liberated from metal phosphides rather more readily by acids than by water.

4 HUMAN HEALTH HAZARD ASSESSMENT

In this report, only summaries are given. A more extensive description of the studies and of the observed findings is included in the draft assessment report, which is attached to the IUCLID dossier and available under http://dar.efsa.europa.eu/dar-web/provision.

The assessment presented in the following subsections is based on the notion that the toxicity of metal phosphides is primarily characterised by the effects caused by liberation of hydrogen phosphide (PH_3) gas. For this reason, studies performed with other metal phosphides, or PH_3 itself were considered adequate for assessing the toxicity of calcium phosphide.

In case of conversion the doses of metal phosphides or PH_3 into calcium phosphide it has to be considered that the different metal phosphides release different maximum amounts of phosphine (due to different mass fraction of phosphor in the respective compounds). Please see below.

Table 14: Metal phosphides

Metal phosphide	Molecular formula	Molecular weight [g/mol]	Phosphor [%]	Max. amount of PH_3 [g PH_3/g metal phosphide]	1 g metal phosphide equiv. to x g calcium phosphide
Calcium phosphide	Ca_3P_2	182.19	34.0	0.37	1
Aluminium phosphide	AlP	57.95	53.4	0.59	1.59
Magnesium phosphide	Mg_3P_2	134.86	45.9	0.50	1.35
Zinc phosphide	Zn_3P_2	258.09	24.0	0.26	0.70

No toxicological studies were performed with impurities. Compared to the very high acute toxicity of phosphine the toxicological properties of impurities are probably negligible.

Unless otherwise noted, studies were conducted under GLP conditions.

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

Studies concerning absorption, distribution, metabolism and excretion of ingested zinc phosphide and phosphine are available. Once formed from the metal phosphide, phosphine is rapidly and completely excreted by exhalation or via urine after oxidation to hypophosphite or phosphite. The phosphine metabolites hypophosphite or phosphite are regarded as less toxic than phosphine itself. Due to the inorganic nature of the metal phosphides and its degradation products and their respective metabolites it is reasonable to assume that residues of these phosphides are expected to be minimal or non-existent. Following oral administration of zinc phosphide, [^{32}P] was rapidly absorbed from the gastrointestinal tract. Inhaled PH_3 is considered to be rapidly and quantitatively absorbed through the lungs. [^{32}P] was detectable in all organs and tissues, with temporary higher levels in liver and medulla oblongata. PH_3 is excreted as such with the expired air or, after metabolic oxidation, with the urine in the form of hypophosphite and phosphite.

In the absence of experimental data, for dermal absorption of both calcium phosphide and PH_3 a default value of 10 %, based on expert judgement, was assumed.

Table 15: Summary of toxicokinetic studies

Method/ Guideline	Route	Species, Strain, Sex, No/group	Dose levels, Duration of exposure	Results	Reference
No guideline; Non-GLP	Oral	Rats, number, bw and sex not stated	Zinc phosphide 40 mg/kg bw (> LD_{50}) and lower dose (not specified), single application	Mortality↑ at high dose, PH_3 detectable in liver	Curry, A.S. et al. (1959) (TOX2002-163)
		Rats, sex not stated, 6 animals	Zinc phosphide 10 mg/rat, single application	Mortality↑, phosphide and PH_3 detectable in liver	
		Rats and guinea pigs, no further information given	No information given	Urinary excretion: main product is hypophosphite	
No guideline, Non-GLP	Oral, subcutan-eous, per rectum	Rattus norvegicus Berk, number, bw and sex not stated	Zinc phosphide, [^{32}P]-labelled 40 mg/kg bw	Oral application: After 6-8 h, ^{32}P was detectable in all organs and tissues with temporary higher levels in liver and medulla oblongata. Application per rectum: After 24 h ^{32}P was detectable in large intestine, arterial blood, liver and kidneys. Subcutaneous injection: After 24 h ^{32}P was detectable only around the point of injection	Andreev, S.B. et al. (1958) (TOX2002-165)
	Oral		Zinc phosphide, ^{32}P- and ^{65}Zn-labelled Sublethal, lethal, 2-, 3- and 4-fold lethal doses	The distribution of ^{32}P was similar to that in the above experiment. ^{65}Zn was found in all organs. The ratio of ^{32}P to ^{65}Zn was different in different tissues.	
No guideline, Non-GLP	oral	Human	Unknown quantity of Phostoxin tablets	Residues post mortem in stomach, blood, liver	Chan, L.T.F. (1983) (TOX98-50056)
Not applicable	Inhalation			Inhaled PH_3 is considered to be readily absorbed through the lungs, excretion with urine as hypophosphite and phosphite and via lungs as PH_3	WHO (1988) (TOX2005-1201)

4.1.2 Human information

Phosphide was detected in post mortem stomach, blood, and liver specimens from the body of a 27-year old man who died after ingestion of an unknown quantity of Phostoxin tablets (Degesch). These 3 g tablets, which contain aluminium phosphide as the active ingredient, slowly produce approximately 1 g phosphine when brought into contact with water. The phosphine was released from the samples after acid treatment and analysed by means of a headspace gas chromatographic technique using a nitrogen phosphorus detector.

4.1.3 Summary and discussion on toxicokinetics

Based on data obtained in experiments with zinc phosphide it is evident that phosphine is rapidly absorbed from the gastrointestinal tract, and rapidly and quantitatively absorbed through the lungs. Phosphine is widely and evenly distributed in the body (temporarily higher levels have been detected in liver and medulla oblongata). It has no potential for accumulation. Phosphine is either excreted as such via the expired air or, after metabolic oxidation, with the urine in form of hypophosphite or phosphite.

4.2 Acute toxicity

4.2.1 Non-human information

The results of the acute toxicity studies including irritancy and skin sensitization are summarised in Table 16.

Table 16: Summary table of relevant acute toxicity studies (LD_{50}/LC_{50} values are reported for the respective test compound)

Method/ Guideline	Species, Strain, Sex, No/group	Dose levels	Value LD_{50}/LC_{50}	Risk Phrase Remarks	Reference
Acute oral toxicity. Similar to OECD 401 Non-GLP	Rat, Wistar albino 5M+5F	Aluminium phosphide 7.94-8.92-10.0-11.2 mg/kg bw	LD_{50} M+F: 8.7 mg/kg bw	R 28 H300	Sterner, W., Stiglic, A. (1977) (TOX2006-981)
Acute dermal toxicity. OECD 402	Rat, Wistar albino 5M+5F	Aluminium phosphide 500-1000-2000 mg/kg bw	LD_{50} M+F: 900 mg/kg bw	R 21 H311	Dickhaus, S., Heisler, E. (1987) (TOX2000-93)
Acute dermal toxicity OPPTS 870.1200	Rat Wistar, 5 F/each level + 5 M/highest level	Aluminium phosphide 0-280-420-630 mg/kg bw	LD_{50}: 461.2 mg/kg bw	R 21 H311	Stephen F. (2000) (TOX2006-213)

Acute dermal toxicity. No guideline Non-GLP	Rat Wistar, 5M+5F	Aluminium phosphide 0-637.7-1275-2550 mg/kg bw	LD_{50}: 901 mg/kg bw	R 21 H311	Joshi M. (1998) (TOX2006-214)
Inhalation whole body 6 h exposure, US EPA	Rat Fisher 344	PH_3 2.4-4.9-11 ppm	LC_{50} M+F: >11 ppm equivalent to > 0.015 mg/L or > 0.675 mg/kg bw	R 26 H330	Newton, P.E. (1989) (TOX97-51198)
Acute inhalation toxicity, whole body, 1 h exposure Similar to OECD 403 Non-GLP	Rat, Slc:SD 10M+10F	PH_3, developed from magnesium phosphide 150-165-182-200-220-242 ppm	LC_{50}: 204/179 ppm (M/F) equivalent to [2]: 0.29/0.25 mg/L air (M/F) or [3] 12.9/11.4 mg/kg bw (M/F)	(R 26, PH_3) [1] H330	Shimizu, Y. et al. (1982) (TOX2005-280)

(1) PH_3 was included into Annex I to Directive 67/548/EEC with R 26, whereas the different phosphides were not classified for inhalation toxicity.

(2) 1 ppm PH_3 is equivalent to 1.41 µg/L air, density of pure PH_3 (20 °C): (34 g/mol)/(24.1 L/mol) = 1.41 g/L

(3) Assuming an hourly respiratory volume (rat) of 45 L/(h kg bw)

4.2.1.1 Acute toxicity: oral

There is no need for an amendment of the current classification, because no new data on acute oral toxicity are available.

No acute oral toxicity study for calcium phosphide has been submitted. However, there exist respective studies with other phosphides: Metal phosphides in contact with moisture (GI tract) readily decompose to metal or calcium hydroxide and phosphine, the toxicological principle. Due to the decomposition by moisture other phosphides are regarded as adequate model compounds. Studies with aluminium phosphide are available and are considered to be of high toxicity when administered orally to animals. The calculated oral LD_{50} of 8.7 mg/kg bw is equivalent to 13.83 mg/kg bw calcium phosphide. Therefore calcium phosphide has to be classified as 'Fatal if swallowed' (Acute Tox. 2; H300) and 'Very toxic if swallowed' (T+; R28) resp..

Report: Sterner, W., Stiglic, A. (1977): Acute oral toxicity of 'Aluminium phosphide' in rats, International Bio-Research, Hannover, Germany; unpublished report no. 0-0-51-77, 01/1977 (TOX2006-981)

Guidelines: No

Deviations: Exceeded application volume.

GLP: No

Acceptability: The study is considered to be acceptable.

Materials and methods:

A single oral dose of aluminium phosphide (technical grade) was given to 5 male and 5 female SPF-Wistar rats/dose group by stomach tube. The body weight of the rats was 140-175 g prior to dosing. In order to apply aluminium phosphide, it was mixed with vaseline to yield a concentration of 1 %. Before use this preparation was suspended in anhydrous olive oil to obtain a final concentration of 0.1 % (no information is given whether this refers to w/v or v/v). The doses administered were 7.94, 8.92, 10.00, and 11.2 mg aluminium phosphide/kg bw. Different doses were applied using different volumes of the test suspension described above. The recommended application volume of 10 mL/kg bw was exceeded. Clinical signs, mortality and body weights were recorded. All surviving animals were sacrificed after 7 days. Macroscopic examinations of all animals were performed and gross pathologic changes were reported.

Findings:

At a dose of 7.94 mg aluminium phosphide/kg bw, 1/5 males and 1/5 females died within day 1, at 8.92 mg/kg bw 3/5 males and 3/5 females died, and at 10.0 mg/kg bw and above all animals died. Survivors recovered by day 2 p.a.. No effect on body weight gain was observed among survivors throughout the post-exposure period. The oral LD_{50} for aluminium phosphide was calculated to be 8.7 mg/kg bw for both sexes.

Table 17: Acute oral toxicity of aluminium phosphide in rats

Dose [mg/kg bw]	Number of dead / number of inves-tigated	Time of death (range)	Observations
7.94	1/5 females 1/5 males	Day 1 Day 1	decreased motor activity, coordination disturbance, abnormal body posture, decreased grip- and limb tone, decreased reflex excitability, tremor, exophthalmus and diarrhea; body weight gain of survivors was unaffected; necropsy findings: swollen liver observed in all animals and serious redness of intestinal mucous membrane in animals that died *post applicationem*
8.92	3/5 females 3/5 males	Day 1 Day 1	the same symptoms as described above but more pronounced; body weight gain of survivors was unaffected; necropsy findings: swollen liver observed in all animals and serious redness of intestinal mucous membrane in animals that died *post applicationem*
10.0	5/5 females 5/5 males	Day 1 Day 1	the same symptoms as described above but more pronounced; necropsy findings: swollen liver observed in all animals and serious redness of intestinal mucous membrane in animals that died *post applicationem*
11.2	5/5 females 5/5 males	Day 1 Day 1	the same symptoms as described above but more pronounced; necropsy findings: swollen liver observed in all animals and serious redness of intestinal mucous membrane in animals that died *post applicationem*
LD_{50} value males + females: 8.7 (8.2 – 9.3) mg/kg bw			

Conclusion:

The LD_{50} for aluminium phosphide in albino rats was calculated as 8.70 (8.17 – 9.27) mg/kg bw for males and females by oral administration.

4.2.1.2 Acute toxicity: inhalation

PH_3, which is developed after contact of calcium phosphide with water by spontaneous hydrolysis of the phosphide, is very toxic by inhalation and according to CLP Regulation classification as 'Fatal if inhaled' (Acute Tox. 2; H330) and 'Very toxic by inhalation' (/T+; R26) resp., is appropriate. Calcium phosphide itself is like aluminium phosphide not classified with regard to inhalation toxicity.

Because of calcium phosphide liberates a toxic gas in contact with water the Suppl. Hazard statement Code (EUH029; R29) is appropriate.

There is no need for an amendment of the current classification, because no new data are available.

4.2.1.3 Acute toxicity: dermal

No dermal toxicity study on calcium phosphide has been submitted but on aluminium phosphide. Regarding calcium phosphide no higher acute dermal toxicity than observed in aluminium phosphide e.g. is expected (LD_{50} 460 – 900 mg/kg bw aluminium phosphide, equivalent to 731.4 – 1431 mg/kg bw calcium phosphide) and classification as 'Toxic in contact with skin (Acute Tox. 3; H311) and 'Harmful in contact with skin' (Xn; R21) is required.

Report:	Dickhaus, S., Heisler, E. (1987): Acute toxicological study on compound aluminium phosphide after dermal application to the rat, pharmatox, Hanover, Germany, unpublished report no. 1-4-142-87, 09/1987 (TOX2000-93)
Guidelines:	Although the test facility claims that this study was conducted according to OECD guideline 404, it complies with OECD guideline 402
Deviations:	Neither purity or batch of test material were mentioned.
GLP:	Yes
Acceptability:	The study is considered to be supplementary.

Materials and methods:

A single dermal dose of aluminium phosphide (purity/batch not mentioned) was applied to the clipped skin of 5 male and 5 female SPF-Wistar rats/dose group under occlusive conditions. Dose levels of 500, 1000 and 2000 mg aluminium phosphide/kg bw were tested. Initial body weights of the rats were 206 – 230 g for males and 202 – 212 g for females, resp.; no information is given about the age of the animals. Prior to application solid granules of aluminium phosphide were minced. Deviating from applicant's study summary it remains unclear from the original study report, whether the test substance was applied as a powder or whether it had been moistened before. No information is provided about the size of the skin area treated with aluminium phosphide. The skin was exposed to the substance for 24 hours. Afterwards residual test substance was removed from the skin using a wet-warm towel and the animals were observed for deaths, clinical signs and body weight gain for 14 days. At the end of the study the remaining rats were sacrificed and all

animals were examined macroscopically for pathological findings. The method of calculating LD_{50} was not mentioned but it was performed in combination with Gauss‘ integral method.

Findings:

No death occurred at 500 mg aluminium phosphide/kg bw; while at a dose of 1000 mg/kg bw, 3/5 males and 3/5 females died and all animals died at 2000 mg/kg bw. No information is given concerning recovery of survivors. Body weight gain was gradually reduced at increasing aluminium phosphide dose levels. The dermal LD_{50} of aluminium phosphide was calculated to be 1520 mg/kg bw (24 hours) or 900 mg/kg bw (day 14) for both sexes by the applicant. Assuming that aluminium phosphide had been applied to the skin as crystalline granules (see above) it would not have adhered just as well on the skin as if a fluid had been applied (apart from the fact that phosphine gas would have been developed simultaneously), i. e. higher doses would have been needed in the first way to yield the same effects as in the latter and a lower LD_{50} would be expected. Nevertheless, it is unlikely that this would have led to a different classification.

Conclusion:

The dermal LD_{50} of aluminium phosphide was calculated to be 1520 mg/kg bw (24 hours) or 900 mg/kg bw (day 14) for both sexes in rats. Accordingly, classification as ‘Toxic in contact with skin (Acute Tox. 3; H311) and ‘Harmful in contact with skin’ (Xn; R 21) resp., is required.

Report:	Stephen, F. (2000): Acute dermal toxicity study of aluminium phosphide technical in rats. JAI Research Foundation (JRF), Gujarat, India, JRF study No. 2566, date 23.10.2000 (TOX2006-213)
Guidelines:	OPPTS 870.1200
Deviations:	Concentration, homogeneity and stability of the dose preparations were not determined. However, the doses were prepared freshly prior to dosing. Batch of test substance was not reported. Environmental conditions like air changes and photoperiod were not reported. Temperature of the experimental animal room was higher during the study (27-28 °C) instead of the recommended 20 ± 3 °C.
GLP:	Yes (laboratory certified by The Netherlands authorities)
Acceptability:	The study is considered to be supplementary.

Materials and Methods:

Following a range-finding preliminary test with 1 male and 1 female per group in which mortalities of 0 %, 50 % and 100 % were observed at dose levels of 250, 500 and 1000 mg/kg bw, resp., rats (Wistar, breeding facilities at JAI Research Foundation, India) were assigned to the test groups (see Table B.6.2-10). One day prior to dosing, the fur was clipped from the dorsal area of the trunk of each animal. The clipped area accounted approximately 10 % of each animal’s body surface. The test substance (purity 85.65 %) was administered as a single occluded dermal application and was applied moistened with peanut oil. After an exposure period of 24 hours, the occlusion was removed and residual test material was removed with dry cotton and tissue paper. Animals were observed for gross toxicity, behavioural changes and/or mortality at approximately 30 minutes, 1, 2, 3 and 5 hours after dermal application and twice daily for the remainder of the 14-day study. Body

weights were recorded at day 0 (prior to dosing), 7 and 14. On day 14, surviving animals were sacrificed and all animals were necropsied and examined for gross pathological changes.

Findings:

Details are provided in Table 18. All early deaths occurred within 48 hours after dermal application.

Table 18: Acute dermal toxicity of aluminium phosphide in rats

	Females		Males	
Dose [mg/kg bw]	**Mortality**	**Time of death**	**Mortality**	**Time of death**
0	--	--	0/5	--
280	--		0/5	--
420	--		2/5	5 hours 30 min (day 1)
630	4/5	4 x 48 hours	4/5	2 x 5 hours 30 min (day 1) 2 x 48 hours
LD_{50} [mg/kg bw]	461.2 (both sexes combined)			

Clinical signs in treated animals on the day of dosing and the day after dosing were lethargy, tremors, abdominal breathing and piloerection. No signs were observed on subsequent days up to the end of the observation period.

All surviving animals showed normal body weight gain following dosing.

Necropsy: No external abnormalities were detected. Vascular/inflammatory alterations in lungs, mottling of liver and hemorrhagic contents in stomach and small intestinal segments were noted in premature decedents. Gross changes observed in the viscera were considered to be associated with terminal sacrifice procedures.

Conclusion:

The acute dermal LD_{50} of aluminium phosphide technical in rats was found to be 461.2 mg/kg bw for both sexes combined.

Report: Joshi, M. (1998): Acute dermal toxicity test of aluminium phosphide technical in rats, JAI Research Foundation (JRF), Gujarat, India, JRF study No. 363, 27.10. 1998 (TOX2006-214)

Guidelines: Gaitonde subcommittee, Central Insecticide Board (CIB), India

Deviations: Concentration, homogeneity and stability of the dose preparations were not determined. However, the doses were prepared freshly prior to dosing. Observation period limited to 7 days. Purity of test substance not mentioned. Age of the animals is not reported. Environmental conditions like air changes and photoperiod were not reported. Temperature of the experimental animal room was higher during the study (27 – 28 °C) instead of the recommended 20 ± 3 °C.

GLP: No

Acceptability: The study is considered to be supplementary.

Materials and Methods:

Wistar rats (breeding facilities at JAI Research Foundation, India) were assigned to the test groups (see Table B.6.2-11). One day prior to dosing, the fur was clipped from the dorsal area of the trunk of each animal. The clipped area accounted not less than 10 % of each animal's body surface. The test substance was administered as a single occluded dermal application and was applied moistened with peanut oil. After an exposure period of 24 hours, the occlusion was removed and residual test material was removed with wet cotton. Animals were observed for gross toxicity, behavioural changes and/or mortality at approximately 1, 2, and 3 hours on the day of dosing and once daily for the remainder of the 7-day study. Body weights were recorded at day 0 (prior to dosing) and 7. On day 7, surviving animals were sacrificed and all animals were necropsied and examined for gross pathological changes.

Findings:

Details are provided in Table 19. All early deaths occurred on the day of dosing.

Table 19: Acute dermal toxicity of aluminium phosphide

	Females		Males	
Dose [mg/kg bw]	**Mortality**	**Time of death**	**Mortality**	**Time of death**
0	0/5	--	0/5	--
637.5	1/5	1-3 hour (day 1)	1/5	1-3 hour (day 1)
1275	4/5	24 hour (day 1)	4/5	24 hour (day 1)
2550	5/5	2 x 1-3 hour (day 1) 3 x 24 hour (day 1)	5/5	1 x 1-3 hour (day 1) 4 x 24 hour (day 1)
LD_{50} [mg/kg bw]	901 (both sexes combined)			

Clinical signs in treated animals on the day of dosing and the day after dosing were lethargy, abdominal breathing, nasal irritation, polyurea, and diarrhoea. No signs were observed on subsequent days up to the end of the observation period.

All surviving animals showed normal body weight gain following dosing.

Necropsy: No external abnormalities were detected. Gross changes observed in the viscera were considered to be associated with terminal sacrifice procedures.

Conclusion:

The acute dermal LD_{50} of aluminium phosphide technical in rats was found to be 901 mg/kg bw for both sexes combined.

4.2.1.4 Acute toxicity: other routes

4.2.2 Human information

No other relevant information is available.

4.2.3 Summary and discussion of acute toxicity

Calcium phosphide is fatal if swallowed (based on read-across from aluminium phosphide: LD_{50} = 8.7 mg/kg bw, equivalent to LD_{50} = 13.83 mg/kg bw calcium phosphide) and toxic in contact with skin (based on read-across from aluminium phosphide: LD_{50} 460 - 900 mg/kg bw, equivalent to LD_{50} = 731.4 - 1431 mg/kg bw calcium phosphide).

Because of calcium phosphide liberates a toxic gas in contact with water the Suppl. Hazard statement Code (EUH029; R29) is appropriate.

4.2.4 Comparison with criteria

The calculated oral LD_{50} value for calcium phosphide is 13.83 mg/kg bw and meets the criteria according to DSD as very toxic (T^+; R28) and according to CLP as fatal if swallowed (Acute Tox. 2; H300).

The calculated dermal LD_{50} value for calcium phosphide is 731.4 – 1431 mg/kg bw and meets the criteria according to DSD as harmful (Xn; R21) and according to CLP as toxic in contact with skin (Acute Tox. 3; H311).

Table 20 presents the toxicological results in comparison with DSD and CLP criteria.

Table 20: Toxicological results in comparison with DSD and CLP criteria

Toxicological result	DSD criteria	CLP criteria
Oral LD_{50}, rat: 8.7 mg/kg (aluminium phosphide) [equivalent to 13.83 mg/kg calcium phosphide]	Very toxic (T+; R28): LD_{50} per oral, rat: $LD_{50} \leq 25$ mg/kg	Cat. 2 (Acute Tox.2; H300): $5 < LD_{50} \leq 50$ mg/kg (oral)
Dermal LD_{50}: 460-900 mg/kg (aluminium phosphide) [eqzuivalent to 731,4 - 1431mg/kg calcium phosphide]	Harmful (Xn; R21): LD_{50} dermal, rat or rabbit: $400 < LD_{50} \leq 2\,000$ mg/kg	Cat. 3 (Acute Tox. 3; H311): $200 < LD_{50} \leq 1\,000$ mg/kg (dermal)

4.2.5 Conclusions on classification and labelling

Calcium phosphide is currently classified as 'Fatal if swallowed" (Acute Tox. 2; H300) and Very toxic if swallowed' (T+; R28). Due to the dermal toxicity of calcium phosphide additional classification as 'Toxic in contact with skin' (Acute Tox. 3; H311) and 'Harmful in contact with skin' (Xn; R21) resp., is required.

RAC evaluation of acute toxicity
Summary of the Dossier submitter's proposal Oral: The substance has a harmonised "minimum" classification of Acute tox. 2* - H300 (Fatal if swallowed) according to the CLP Regulation and a harmonised classification as T^+; R28 (Very toxic if swallowed) according to the DSD. No acute oral toxicity study for tricalcium diphosphide is presented in the CLH report. However, the dossier submitter (DS) considers aluminium phosphide as an adequate compound for read-across to tricalcium diphosphide and, based on the LD_{50} of 8.70 mg/kg bw, equivalemt to 13.83 mg/kg bw tricalcium diphosphide, obtained in a study on rats, proposes to remove the "minimum" classification

and classify as Acute Tox. 2 - H300 (CLP).

Dermal: No harmonised classification is present for this hazard class and no acute dermal study on tricalcium diphosphide is available. However, based on the studies conducted with rats on aluminum phosphide (LD_{50} = 460 – 900 mg/kg bw, equivalent to 731.4 – 1431 mg/kg bw tricalcium diphosphide), the DS proposes to classify the substance as Acute Tox. 3 - H311 (CLP) and Xn; R21 (DSD).

Inhalation: No acute inhalation study on tricalcium diphosphide is available. However, in contact with water tricalcium diphosphide liberates, by spontaneous hydrolysis of the phosphide, phosphine gas (PH_3), which is classified as Acute Tox. 2* - H330 (Fatal if inhaled) and T^+; R26 (Very toxic by inhalation). Therefore the DS considers the harmonised supplemental hazard statement EUH029 (in contact with water liberates toxic gas) as appropriate.

Comments received during public consultation

Oral: Comments were received from one MSCA and one industry representative. Both were in support of the proposal; the industry representative asked for inclusion of an acute oral toxicity study conducted with Wistar rats on Polytanol (17.6% tricalcium diphosphide) in the CLH report. The study is included in the DAR but was not addressed by the DS as it was conducted with a low purity mixture.

Dermal: One comment was received from a MSCA, supporting the proposal to classify for acute dermal toxicity.

Inhalation: Three comments were received on acute inhalation toxicity during public consultation, two from Member States and one from industry. All comments proposed classification for tricalcium diphosphide as Acute Tox. 1 - H330 (Fatal if inhaled) (CLP) and T^+; R26 (Very toxic by inhalation) (DSD). This proposal is based on calculated LC_{50} values obtained from acute inhalation studies using phosphine gas, either pure or liberated from metal phosphides. Two studies are mentioned in the CLH report but two additional studies (Roy, 1998 and Wartz & Brown, 1975), both using aluminium phosphide as the source of phoshine gas) were mentioned during PC. Industry furthermore asked for inclusion of an acute inhalation toxicity study conducted with Wistar rats on Polytanol (17.6% tricalcium diphosphide) in the CLH report. The study is included in the DAR but was not addressed by the DS as it was conducted with a low purity mixture.

One MSCA also commented that the same approach was applied by the RAC to classify aluminium phosphide and trimagnesium diphosphide (opinions published in December 2011 on ECHA website). The draft EFSA Scientific Report (2008) proposed, as well, to classify tricalcium diphosphide as T^+; R26. Two comments proposed supplemental labelling with EUH032 (CLP) and R32 (DSD); one originated from a MSCA and one from industry and were based on the well known chemical properties of tricalcium diphosphide to generate the toxic gas phosphine in contact with acids.

The DS supported the proposal received during public consultation to classify tricalcium diphosphide as Acute Tox. 1 - H330 and T^+; R26 as well as the addition of EUH032 (CLP) and R32 (DSD).

Assessment and comparison with the classification criteria

Oral: The RAC confirmed the classification of tricalcium diphosphide as Acute Tox. 2 - H300 (Fatal if swallowed), according to CLP. (5 mg/kg bw < LD_{50} ≤ 50 mg/kg bw). This

classification is based on the LD_{50} value obtained in one oral toxicity study in rats with aluminium phosphide providing an LD_{50} of 8.7 mg/kg bw (Sterner, 1977), equivalent to 13.8 mg/kg bw of tricalcium diphosphide (conversion factor "1.59" is used).

Dermal: The RAC supported the proposed classification of tricalcium diphosphide as Acute Tox. 3 - H311 (Toxic in contact with skin), according to CLP and as Xn; R21 (Harmful in contact with skin), according to DSD. The respective criterion according to CLP is 200 mg/kg bw < LD_{50} ≤ 1000 mg/kg bw and according to DSD is 400 mg/kg bw < LD_{50} ≤ 2000 mg/kg bw. This classification is based on the LD_{50} values obtained in three acute dermal toxicity studies in rats with aluminium phosphide: LD_{50} = 461.2 mg/kg bw (Stephen, 2000) equivalent to 733.3 mg/kg bw of tricalcium diphosphide, LD_{50}= 900 mg/kg bw (Dickhaus et al., 1987) equivalent to 1431 mg/kg bw of tricalcium diphosphide and LD_{50}= 901 mg/kg bw (Joshi, 1998) equivalent to 1432.6 mg/kg bw of tricalcium diphosphide (using a conversion factor of 1.59). For classification purposes, the lowest LD_{50} value has been used.

Inhalation: The RAC proposed to classifiy tricalcium diphosphide as Acute Tox. 1 - H330 (Fatal if inhaled), according to CLP and T^+; R26 (Very toxic by inhalation), according to DSD. This is in line with the comments received during public consultation. It is based on read-across to, aluminium phosphide and trimagnesium diphosphide, which the RAC concluded should be classified in the same way (see the relevant RAC opinions published in December 2011 on the ECHA website). No acute inhalation study on tricalcium diphosphide is available but, analogous to most other metal phosphides, tricalcium diphosphide liberates toxic phosphine gas in contact with water or moisture. This release will occur in the presence of moisture in the alveoli when metal phosphide dust is inhaled (see e.g. Gehring et al., 1991). LC_{50} gaseous phosphine levels or phosphine levels liberated from aluminium phosphide or trimagnesium diphosphide and converted to tricalcium diphosphide are in the range from 0.04 to 0.19 mg/l (see Table 2). The highest values 0.17-0.19 mg/l were obtained in the study of Shimizu (1982), where 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. In relation to the study of Roy (1998), in which LC_{50} = 0.13 mg Ca_3P_2/l was obtained, the RAC considered the method of measurement as not very well documented.

Taking into account the relevant criteria for for dust inhalation according to the CLP Regulation (LC_{50} ≤ 0.05 mg/l) and according to the DSD (LC_{50} ≤ 0.25 mg/l), classification as Acute Tox. 1 (DSD; T+; R26, Very toxic by inhalation) is proposed.

Moreover, the RAC proposed to add EUH032 under CLP as well as R32 under the DSD (Contact with acids liberates very toxic gas), in line with comments received during public consultation.

Supplemental information - In depth analyses by RAC

Two acute inhalation toxicity studies were brought to the attention of the RAC during PC and two studies were mentioned in the CLH report. Table 2 summarises the results of these studies and reports the calculated LC_{50} values for tricalcium diphosphide. Around 0.37 g of phosphine is liberated from 1 g of tricalcium diphosphide and this is used to calculate the LC_{50} value for tricalcium diphosphide from the LC_{50} value of phosphine gas.

Table 2: Summary of acute inhalation toxicity studies conducted with phosphine gas, either pure or liberated from metal phosphides

Method/ Guideline	**Route**	**Species, Strain, Sex, No/group**	**Dose levels (mg/kg bw)**	**PH_3 LC_{50} (ppm) (mg/l air /4h)**	**Calculated LC_{50} of Ca_3P_2 (assuming 100% hydrolysis reaction to PH_3) (2)**	**Reference**
Not mentioned, Non-GLP	Inhalation, whole body, 4 hours exposure to gaseous phosphine	Rat, ChR-CD 6M+0F	PH_3 Dose levels not reported	LC_{50} M: 11 ppm equivalent to (1): 0.015 mg PH_3 /l air	0.04 mg Ca_3P_2/L	Waritz, R.S. and Brown R.M. (1975); Amer. Ind. Hyg. Assoc. J., p 452
No guideline, non GLP	Inhalation, head only exposure chamber Exposure most probably to gaseous phosphine and aerosol of AlP	Rat Wistar, 5M+5F	PH3, generated from aluminium phosphide 0-15.4-26-47 ppm	LC_{50} M+F: 34.6 ppm equivalent to (1): 0.048 mg PH_3/l	0.13 mg Ca_3P_2/l	Roy, B.C. (1998) TOX2006-215
Similar to OECD 403, Non-GLP	Inhalation, whole body, 1 h exposure to gaseous phosphine generated by reaction of magnesium phosphide and distilled water	Rat, Slc:SD 10M+10F	PH_3, generated from trimagnesium diphosphide 150-165-182-200-220-242 ppm	M+F 204/179 ppm equivalent to (1): 0.29/0.25 mg PH_3/l air (M/F) calculated for 4 hour exposure 0.072mg PH_3/l for males or 51 ppm calculated for 4 hour exposure 0.063mg PH_3/l for females or	0.19 mg Ca_3P_2/L for males 0.17 mg Ca_3P_2/L for females	Shimizu, Y. et al. (1982), report no. NRI 82-7489

				44 ppm		
US EPA 81-3	Inhalation, whole body, 6 h exposure to gaseous phosphine	Rat Fisher 344 15M+15F	PH3 2.4-4.9-11 ppm	LC50 M+F: >11 ppm equivalent to > 0.015 mg/l	> 0.04 CaP mg/l	Newton, P.E. (1989) (TOX97-51198)

(4) 1 ppm PH_3 is equivalent to 1.41 µg/l air, density of pure PH_3 (20 °C): (34 g/mol)/(24.1 L/mol) = 1.41 g/l

(5) Assuming full hydrolysis, 1 g CaP releases 0.37g PH_3

4.3 Specific target organ toxicity – single exposure (STOT SE)

There is no evidence of specific target organ toxicity after single exposure of calcium phosphide

4.3.1 Summary and discussion of Specific target organ toxicity – single exposure

No toxicity to a specific organ in the absence of lethality was observed in acute oral, inhalation or dermal toxicity studies. There are no relevant data to discuss specific target organ toxicity after single exposure.

4.3.2 Comparison with criteria

There are no relevant data to compare with criteria.

4.3.3 Conclusions on classification and labelling

Classification and labelling is not needed.

4.4 Irritation

Table 21: Summary table of skin irritation studies

Method/ Guideline	Species, Strain, Sex, No/group	Dose levels	Result	Risk Phrase Remarks	Reference
Acute skin irritation. Partly OECD 404	Rabbit, White New Zealand, 5 (sex not mentioned)	Aluminium phosphide 0.5 g/animal	Not irritating	None	Dickhaus, S., Heisler, E. (1987) (TOX2000-94)
Acute skin irritation. No guideline, non-GLP	Rabbit, White New Zealand, 3M+3F	Aluminium phosphide 0.5 g/animal	Non-irritating	None	Joshi M. (1998) (TOX2006-216)
Acute skin irritation.	Rabbit, New Zealand	Zinc phosphide 0.5 g/animal	Not irritating	None	Brunt, P. (2001)

OECD 404	White 3M				(TOX2005-168)

4.4.1 Skin irritation

4.4.1.1 Non-human information

No skin irritation study for calcium phosphide has been submitted. Studies on aluminium and zinc phosphide revealed no skin-irritating potential. Calcium phosphide in contact with moisture readily decomposes to calcium hydroxide and phosphine. The pH of calcium hydroxide is between 12 and 13 and corrosive effects are expected. The Registration Dossier published on ECHA homepage revealed that irritating effects for calcium hydroxide [in putty form: 60 % H_20, 40 % Ca(OH)2] were observed in rabbits.

Based on the formation of calcium hydroxide, calcium phosphide should be considered as a corrosive substance and classification as 'Skin Corr. 1A; H314' (C; R35) is proposed.

4.4.1.2 Human information

No other relevant data available.

4.4.1.3 Summary and discussion of skin irritation

No skin irritation study for calcium phosphide has been submitted. Due to expected corrosive effects of the hydrolysis product calcium hydroxide and observed irritating effects in rabbits after dermal administration of 40 % $Ca(OH)_2$ in putty form also calcium phosphide should be considered as a corrosive substance.

Classification and Labelling for skin corrosion/irritation according to Directive 67/548/EEC:

C; R35 (Causes severe burns)

Classification and Labelling for skin corrosion/irritation according to GHS:

Skin Corr. 1A; H314 (Causes severe skin burns and eye damage)

4.4.1.4 Comparison with criteria

The pH of the hydrolysis product calcium hydroxide is ≥ 11.5 (between 12 and 13) and therefore, corrosive effects are expected. Additionally, the Registration Dossier published on ECHA homepage revealed that an irritating potential for calcium hydroxide [putty form: 60 % H_20, 40 % $Ca(OH)_2$] was observed in rabbits.

4.4.1.5 Conclusions on classification and labelling

Due to the skin burn potential of its hydrolysis product (calcium hydroxide) calcium phosphide should be classified as corrosive.

4.4.2 Eye irritation

Table 22: Summary table of eye irritation studies

Method/ Guideline	Species, Strain, Sex, No/group	Dose levels	Result	Risk Phrase Remarks	Reference
Acute eye irritation OECD 405	Rabbit White, New Zealand 6 (sex not mentioned	Aluminium phosphide 0.1 g/animal	Non-irritant (washed out 30 seconds after application)	Study design not suitable	Dickhaus, S., Heisler, E. (1987) (TOX2000-95)
Acute eye irritation. No guideline, non-GLP	Rabbit, White New Zealand, 3M + 3F	Aluminium phosphide 1 mg/animal	Not acceptable	Study design not suitable	Joshi, M. (1998) (TOX2006-217)
Acute eye irritation OECD 405	Rabbit, White New Zealand, 2M+1F	Zinc phosphide 0.1 mL/animal	Non-irritant	None	Brunt, P. (2001) (TOX2005-171)

4.4.2.1 Non-human information

No eye irritation study for calcium phosphide has been submitted. A guideline-conform study on zinc phosphide revealed no eye-irritating potential. Calcium phosphide in contact with moisture readily decomposes to calcium hydroxide and phosphine. The pH of calcium hydroxide is ≥11.5 (between 12 and 13) and therefore, corrosive effects are expected. Furthermore, the Registration Dossier published on ECHA homepage revealed that an irritating potential for calcium hydroxide [putty form: 60 % H_2O, 40 % $Ca(OH)_2$] was observed in rabbits.

Based on the formation of calcium hydroxide, calcium phosphide should be considered as a corrosive substance and classification as Skin Corr. 1A (H314) and C; R35 resp., is proposed. If a substance is classified as Skin corrosive Cat. 1 then serious damage to eyes is implicit.

4.4.2.2 Human information

No other relevant data available.

4.4.2.3 Summary and discussion of eye irritation

No eye irritation study for calcium phosphide has been submitted. Based on the pH value of ≥ 11.5 for the hydrolysis product calcium hydroxide, calcium phosphide should be considered as corrosive substance. Due to expected corrosive effects of calcium hydroxide and observed irritating effects in rabbits after dermal administration of 40 % $Ca(OH)_2$ [putty form] calcium phosphide should be considered as a corrosive substance as well. If a substance is classified as Skin corrosive Cat. 1A then serious damage to eyes is implicit.

Classification and Labelling for corrosion/irritation according to Directive 67/548/EEC:

C; R35 (Corrosive; Causes severe burns)

Classification and Labelling for corrosion/irritation according to GHS:

Skin Corr. 1A; H314 (Causes severe skin burns and eye damage)

4.4.2.4 Comparison with criteria

The pH of the hydrolysis product calcium hydroxide is ≥ 11.5 (between 12 and 13) and therefore, corrosive effects are expected. Furthermore, the Registration Dossier published on ECHA homepage revealed that an irritating potential for calcium hydroxide [in putty form: 60 % H_2O, 40 % $Ca(OH)_2$] was observed in rabbits.

4.4.2.5 Conclusions on classification and labelling

Due to the corrosive potential of its hydrolysis product (calcium hydroxide) calcium phosphide should be classified as corrosive.

4.4.3 Respiratory tract irritation

No data available.

4.5 Corrosivity

4.5.1 Non-human information

No data available.

4.5.2 Human information

No data available.

4.5.3 Summary and discussion of corrosivity

Based on the extreme pH of ≥11.5 of the hydrolysis product calcium hydroxide and its irritating effects after dermal administration (40 % in putty form) in rabbits the main substance calcium phosphide should be considered as a corrosive substance.

4.5.4 Comparison with criteria

The pH of the hydrolysis product calcium hydroxide is ≥ 11.5 (between 12 and 13).

4.5.5 Conclusions on classification and labelling

Due to corrosive potential of its hydrolysis product (calcium hydroxide) calcium phosphide should be classified as corrosive.

RAC evaluation of irritation/corrosion
Summary of the Dossier submitter's proposal No irritation or corrosion studies for tricalcium diphosphide are reported in the CLH dossier. However, due to the expected corrosive properties of calcium hydroxide (hydrolysis product of tricalcium diphosphide, pH between 12 and 13), the DS proposed to classify tricalcium diphosphide as Skin Corr. 1A; H314 (Causes severe skin burns and eye damage) according to

CLP, and as C;R35 (Causes severe burns) according to DSD.

Comments received during public consultation

Three comments were received during public consultation, two from Member States and one from industry. One Member State and Industry objected to the proposed classification and instead proposed to classify as Skin Irrit. 2; H315 (Causes skin irritation), as Eye Dam. 1; H318 (Causes serious eye damage) and as STOT SE 3; H335 (May cause respiratory irritation) according to the CLP criteria, and as R37/38 (irritating to respiratory system and skin) and R41 (risk to serious damage to eye) according to the DSD criteria. This is based on the low alkaline reserve of calcium dihydroxide (Young et al, 1998) and irritating effects of a product containing calcium carbide (which also hydrolyses to calcium dihydroxide) (Moeller, 2011). The second Member State suggested to the RAC to conduct a thorough evaluation of skin irritation/corrosion based on the classification proposal for calcium dihydroxide in the REACH registration dossier (Skin Irrit. 2 - H315, Eye Dam. 1 - H318 and STOT SE 3 - H335). Further details can be found in the RCOM.

The DS maintained the original proposal and welcomed a RAC discussion on the matter.

Assessment and comparison with the classification criteria

No skin or eye irritation study for tricalcium diphosphide has been submitted. The available reports on aluminium phosphide and zinc phosphide show that these metal phosphides are not skin and eye irritants.

In contact with moisture, Tricalcium diphosphide readily decomposes to calcium hydroxide and phosphine. The established irritating or corrosive properties of calcium hydroxide can therefore be used for classification of tricalcium diphosphide. The pH of calcium hydroxide is > 11.5. According to point 3.2.2.2 of CLP "*pH extremes like ≤ 2 and ≥ 11.5 may indicate the potential to cause skin effects … If consideration of alkali/acid reserve suggests the substance may not be corrosive despite the low or high pH value, then further testing shall be carried out to confirm this*". The registration dossiers for calcium dihydroxide published on the ECHA website provide a number of reports on skin and eye irritation. Two key studies on rabbits regarding skin irritation, performed according to OECD TG 404 are reported in the registration dossier. In one study, 0.5 g of calcium hydroxide was applied in a powder form but no moistening was applied and the study is not considered reliable by the RAC for this reason. In another study 0.5 g of a putty containing 40% calcium hydroxide mixed with water was applied to three animals. Some symptoms of irritation were observed during the observation period when the "putty" form of calcium hydroxide was applied. The mean (from gradings at 24, 48 and 72 hours) skin erythema scores were 2, 2 and 0 and oedema scores were 1, 0, 0. 14 days after the termination of exposure all animals were free of any skin reactions. In addition, an acute dermal toxicity study on calcium hydroxide reported in the registration dossier for calcium hydroxide, shows some skin irritating effects. When calcium hydroxide (concentration unknown) was applied under semi-occlusion for 24 h, a mean erythema/eschar score of approx. 2 was calculated (10 rabbits used). Observation period was 14 days but reversibility was not reported nor the timing of scores used for calculating mean erythema scores.

According to the CLP criteria, mean erythema/oedema scores of ≥ 2,3 - ≤ 4,0 for at least 2 out of three animals tested are sufficient for Skin Irrit. 2. For classification as Xi; R38 (irritating to skin) under DSD, a substance must show significant inflammation of the rabbit skin which persists for at least 24 hours after an exposure period of up to four hours. Inflammation of the skin is significant if: (a) the mean value of the scores for either erythema and eschar formation or oedema formation, calculated over all the animals tested, is 2 or more; or (b) in the case where the test has been completed using three animals, either erythema and eschar formation or oedema formation equivalent to a mean value of 2 or more

calculated for each animal separately has been observed in two or more animals.

The skin effects seen with the putty form of calcium hydroxide warrant classification as Xi; R38 under DSD . With regards to the CLP criteria, the erythema scores seen with the putty form are below the cut-off value for classification as Skin Irrit. 2 - H315. While there are indications of irritation in the acute dermal toxicity study on calcium hydroxide, the long exposure period and the limited reporting do not allow for using the study as supporting evidence for classification.

As regards eye irritation, two key studies on rabbits using calcium hydroxide and performed according to OECD TG 405 were reported in the REACH registration dossier of calcium hydroxide. Very severe eye reactions were observed 1 hour after application of 0.1 g of calcium hydroxide to the rabbit eye, with pronounced chemosis (score: 3), necrotised appearance of the conjunctiva, whitish watering and total opacity of the cornea, showing nacreous appearance (further information can be found in the supplemental information section in the background document).

According to the CLP and DSD criteria, classification into category Eye Dam. 1 - H318 and Xi;R41, respectively, is valid if: (a) at least in one animal effects on the cornea, iris or conjunctiva are not expected to reverse or have not fully reversed within an observation period of normally 21 days and/or (b) at least in 2 of 3 tested animals, a positive response of corneal opacity ≥ 3 and/or iritis > 1.5 (>2 in the DSD) calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material.

Based on the study results given in the REACH registration dossier calcium dihydroxide would be classified as Eye Dam. 1 - H318 (Causes serious eye damage) according to CLP and Xi; R41 (Risk of serious damage to eyes) according to the DSD.

On the basis of the argumentation above and using evidence from calcium hydroxide, a product of tricalcium diphosphide decomposition in contact with water, the RAC did not support the proposed classification as Skin Corr. 1A - H314 (CLP) and C;R35 (DSD). The RAC concluded that the information provided in the CLH report and during public consultation is insufficient to conclude on classification for skin irritation according to the CLP criteria and proposed no classification. However, the RAC concluded that tricalcium diphosphide should be classified as irritant under the DSD and proposed classification as Xi;R38. Furthermore, the RAC concluded that tricalcium diphosphide should be classified as Eye Dam. 1 - H318 (Causes serious eye damage) according to CLP and Xi; R41 (Risk of serious damage to eyes) according to DSD.

Supplemental information - In depth analyses by RAC

Two key studies on rabbits regarding eye irritation were performed according to OECD TG 405 given in the REACH registration dossier for calcium dihydroxide (available on the ECHA website under Information on chemicals/Registered substances).

In the first study a single dose of 0.1 ml of the product (150 g/l Calcium hydroxide suspension) as such was introduced in the conjunctival cul-de-sac of the left eye of the 3 animals. The eyes were examined about 1 hour, 24, 48 and 72 hours after administration of the product. As there were signs of persistent eye irritancy after 72 hours, the period of observation was extended by 21 days maximum (until day 22), to determine the progress of damage and reversibility or irriversibility thereof. The eyes were not rinsed after administration of the product. Draize scoring system was used.

The following average scores (24, 48, 72 h) for the individual animals have been calculated:

animal no.1: cornea score: 0.3; iris score: 0.7; conjunctivae score: 2.0; chemosis score: 2.0

animal no. 2: cornea score: 0; iris score: 0.7; conjunctivae score: 2.0; chemosis score: 2.0

animal no. 3: cornea score: 2.0; iris score: 1.0; conjunctivae score: 3.0; chemosis score: 3.0

mean scores (24-72 hours) from three animals: cornea score: 0.77; iris score: 0.8; conjunctivae score: 2.3; chemosis score: 2.3.

All ocular effects were usually reversed at the day 7 or 8 with the exception for conjunctival redness and chemosis in animal no. 1 in which not fully reversible effects within observation time were noted.

In the second study a single dose of 100 mg of the product as such (in the form of powder) was introduced in the conjuctival cul-de-sac of the left eye of the animal. Very severe eye reactions were observed 1 hour after the treatment, with pronounced chemosis (score: 3), necrotised appearance of the conjunctiva, whitish watering and total opacity of the cornea, showing nacreous appearance. The iris was no longer visible. Given the seriousness of the eye lesions observed, the animal was put down for animal protection reasons, and the product was not tested on the other two rabbits.

4.6 Sensitisation

Table 23: Summary table of sensitisation studies

Method/ Guideline	Species, Strain, Sex, No/group	Dose levels	Result	Risk Phrase Remarks	Reference
Skin sensitisation OECD 406	Albino Guinea Pig (10M)	Zinc phoshpide	Non-sensitising	None	Brunt, P. (2001) (TOX2002-179)

4.6.1 Skin sensitisation

4.6.1.1 Non-human information

No skin sensitisation study has been presented using calcium phosphide. However, the study for zinc phosphide revealed no skin sensitisation potential. Therefore, calcium phosphide is not considered a sensitiser, and classification and labelling is not required.

4.6.1.2 Human information

No data available.

4.6.1.3 Summary and discussion of skin sensitisation

Calcium phosphide is not considered a sensitiser.

4.6.1.4 Comparison with criteria

There are no relevant data to compare with criteria.

4.6.1.5 Conclusions on classification and labelling

Classification and labelling is not needed.

4.6.2 Respiratory sensitisation

4.6.2.1 Non-human information

No experimental data are available.

4.6.2.2 Human information

Respiratory sensitisation in humans has not been reported while metal phosphide rodenticides/ insecticides have been produced and marketed for decades.

4.6.2.3 Summary and discussion of respiratory sensitisation

Calcium phosphide is not considered a sensitiser.

4.6.2.4 Comparison with criteria

There are no relevant data to compare with criteria.

4.6.2.5 Conclusions on classification and labelling

Classification and labelling is not needed.

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)
Summary of the Dossier submitter's proposal No toxicity to a specific organ in the absence of lethality was observed in acute oral, inhalation or dermal toxicity studies. No classification was proposed by the DS. **Comments received during public consultation** One MSCA proposed to consider classification as STOT SE 3, H335 according to the CLP Regulation and as R37/38-41 according to the DSD. The classification was proposed in the context of the irritant properties of tricalcium diphosphide to skin and eye but no specific justification was given. Similarly, another MSCA, while considering classification of irritant properties of tricalcium diphosphide, also proposed a classification as STOT SE 3 - H335, in this case without comparison with the classification criteria. In response to these suggestions the DS proposed that it would be appropriate for RAC to discuss these proposals in Committee.

Assessment and comparison with the classification criteria

In the absence of data on respiratory tract irritation after single exposure of humans or animals to tricalcium diphosphide at low or moderate concentration, taking into account that the median lethal concentration of this substance is calculated to be 0.04 mg Ca_3P_2/l, it does not appear warranted to assign this substance to category STOT SE 3 - H335 (Xi; R37/38-41 under DSD).

Having in mind that there are no human or animal data which could be compared with the criteria for respiratory tract irritation set in section 3.8.2.2.1 of Annex I to the CLP Regulation, the RAC was of the opinion that classification of tricalcium diphosphide to STOT SE 3 - H335 is not justified. The irritant properties of this substance or its decomposition products are sufficiently covered in other hazard classes. In addition, a hazard linked with single acute inhalation exposure is adequately communicated by the classification as Acute Tox. 1 - H330 (T^+; R26 under DSD) and the supplemental labelling EUH029 (Contact with water liberates toxic gas).

4.7 Repeated dose toxicity

4.7.1 Non-human information

The results of the repeated dose toxicity studies are summarised in Table 24.

Table 24: Summary table of relevant repeated dose toxicity studies

Method/ Guideline	Species, Strain, Sex, No/group	Dose levels	Value NOAEL	Reference
Subchronic, oral, 13 week, Non-GLP	Rat, CFT-Wistar, 12F (female only)	Zinc phosphide 0, 50, 100, 200, 500 ppm	< 50 ppm (3.5 mg/kg bw/d)	Muktha Bai, K. et al. (1980), (TOX 2005-175)
Subchronic, oral, 90 d Non-GLP	Rat, Wistar 24M+24F 32M+32F (control)	Aluminium phosphide 0, 0.1, 0.5, 2 (week 1 and 2) 1 mg/kg bw	1 mg/kg bw (0.59 mg PH_3/kg bw)	Schnellhardt, M. et al. (1985), (TOX2005-282)
Subchronic, inhalation, 6h/day, 5d/week, 2 wks, Non-GLP	Rat, Fischer 344; Mouse, B6C3F1, 6M+6F	Phosphine gas (PH_3) 0, 1.25, 2.5, 5 ppm	2.5 ppm = 0.95 mg/kg bw (rat) 0.1 mg/kg bw (mice)	Morgan, D.L. et al. (1995) (TOX2002-181)
Subchronic, inhalation, 6h/day, 5d/week, 2 – 4 wks, Non-GLP	Mouse, ICR, 10M	Phosphine gas (PH_3) 5 ppm	No reliable NOAEL can be derived. Study not acceptable	Omae, K. et al. (1996) (TOX2002-174)
Subchronic, inhalation, 6h/day, 5d/week, 13 wks, satellite groups 3 resp. 13 days OECD 413; GLP	Rat, Fischer 344, 30M+30F, satellite 10M+10F and 6M+6F (control)	Phosphine gas (PH_3) 0, 0.3, 1, 3, satellite groups: 5, 10 ppm	3 ppm = 1.1 mg/kg bw	Newton, P.E. (1990) (TOX2001-684)

Subchronic, inhalation, no guideline, no GLP	Rats (only male), cats and guinea pigs	Phosphine gas (PH_3) 1, 2.5, 5 ppm No control groups!	No NOAEL can be derived. Study is not acceptable.	Klimmer, O.R. (1969), (TOX 96-52057)

1 ppm PH_3 is equivalent to 1.41 µg/L air, density of pure PH_3 (20 °C): (34 g/mol)/(24.1 L/mol) = 1.41 g/L Assuming an hourly respiratory volume (rat) of 45 L/(h kg bw)

4.7.1.1 Repeated dose toxicity: oral

In an oral 90-day gavage test, mortality was increased at 2 mg aluminium phosphide/kg bw/d (equivalent to 3.18 mg/kg bw/d calcium phosphide, corresponding to 1.18 mg PH_3/kg bw/d) in both sexes, the NOAEL being 1 mg aluminium phosphide/kg bw/d, equivalent to 1.59 mg/kg bw/d calcium phosphide corresponding to 0.59 mg PH_3/kg bw/d, resp.. However, these values are considered to be of limited reliability due to methodological deficiencies of the respective study report.

Male and female rats and mice were exposed up to 0, 1.25, 2.5 or 5 ppm PH_3 for 2 weeks. Under the conditions of this investigation the NOAEL was determined as 2.5 ppm PH_3 (0.95 mg/kg bw/day for rats, 0.1 mg/kg bw/day for mice, equivalent to 1.51 and 0.16 mg/kg bw/d calcium phosphide) based on decreased lung weights in male rats/mice, increased heart weight in female rats/mice and increased urea nitrogen in mice at 5 ppm PH_3 (1.9 mg/kg bw/day for rats, 0.2 mg/kg bw/day for mice, equivalent to 3.02 and 0.03 mg/kg bw/d calcium phosphide).

In spite of the shortcomings of the database on oral repeat-dose toxicity, no new oral 90-d study was considered necessary based on the following considerations:

- In the acute toxicity studies performed with aluminium phosphide, trimagnesium phosphide, or PH_3, no route-specific differences in toxicity were observed when comparing oral and inhalative uptake,
- the only potential oral uptake scenario is via residues in food, and such residues can be expected to be very low to negligible,
- chronic oral studies using diet fumigated with PH_3 are available, in which no relevant adverse effects were noted. Although these studies themselves are considered to be of questionable reliability, these results suggest that chronic low-level intake of potential residues from PH_3 fumigation via the diet does not raise any specific concern that would justify additional vertebrate testing, and
- due to the toxic mode of action of the metal phosphides/PH_3, species-specific differences do not seem likely and have not been observed in a number of non-guideline experiments.

4.7.1.2 Repeated dose toxicity: inhalation

After inhalative administration of up to 3 ppm PH_3 gas (equivalent to ca. 1.1 mg/kg bw/d) to rats over a period of 90 days, no substance related adverse effects were observed. Two satellite groups at 5 and 10 ppm, resp., were introduced during the course of the study. In the 5 ppm satellite group, which received the test item for only 2 weeks, no relevant effects were observed (which is in accordance with the NOAEL of 4.9 ppm in the inhalative developmental study in rats, see below). Inhalative administration of 10 ppm PH_3 (3.8 mg PH_3/kg/bw/d) was terminated after 3 days, when already 4/10 females had died. In summary, a short-term NOAEL of 1.1 mg PH_3/kg bw/d was established.

A sub-chronic inhalation study in a second, non-rodent species was not submitted. For justification of non-submission please refer to point 4.7.1.6.

4.7.1.3 Repeated dose toxicity: dermal

No experimental animal data are available.

4.7.1.4 Repeated dose toxicity: other routes

No relevant data are available.

4.7.1.5 Human information

No relevant data are available.

4.7.1.6 Other relevant information

Short term toxicity studies in a non-rodent species were not submitted and are not considered to be required for the following reasons:

- The toxic mechanism of magnesium phosphide via hydrolysis to the toxic phosphine gas is well known, involving inhibitory action on enzymes of electron transport mechanisms (IPCS, 1997[1]) and also reaction with haeme proteins (Potter et al. 1991[2]). The mechanism of toxicity can therefore be considered not to be species-specific.
- In view of the inorganic nature of the substance and the need for hydrolysis in the GI tract to elicit any toxicity, there is no reason to assume any relevant difference in uptake and metabolism between species.
- Although only of indicative value, acute toxicity studies in rats, rabbits, guinea pigs, mice, cats and data in humans have yielded acute lethal concentration in a very narrow range, indicating that the species tested are similarly susceptible to phosphine (WHO, 1988[3]; IPCS, 1997[5] Jokote, 1904[4]).
- Similarly steep dose-response curves have been established across a range of species such as cats, rats, rabbits and guinea pigs after sub-acute or sub-chronic exposure (Klimmer, 1969[5]; Müller, 1940[6], Newton, 1993[7]; Okolie et al., 2004[8]). In consideration of the arguments given

[1] IPCS International Programme on Chemical Safety (1997): Poisons Information Monograph 865. Phosphine.

[2] Potter, W.T. et al. (1991): Phosphine-mediated Heinz body formation and haemoglobin oxidation in human erythrocytes. Toxicol. Lett. 57(1), 37-45.

[3] WHO World Health Organisation (1988): Phosphine and selected metal phosphides, IPCS, Environmental Health Criteria 73, WHO, Geneva

[4] Jokote, C.H. (1904): Experimentelle Studien über den Einfluß technisch und hygienisch wichtiger Gase und Dämpfe auf den Organismus, Teil XI. Studien über Phosphorwasserstoff. Arch. für Hyg. 49/50, 275-306.

[5] Klimmer, O.R. (1969): Beitrag zur Wirkung des Phosphorwasserstoffes. Arch. Toxikol. 24 (2), 164-87.

[6] Müller, W. (1940): Über Phosphorwasserstoffvergiftungen (Tierversuche). I. Mitt. Akute und subacute Vergiftung. Naunyn-Schmiedebergs Arch. Exp. Path. Pharmak. 239, 194-193.

[7] IIA 5.2.3/03

above, there is no reason to assume that the dog is more susceptible than the rat to phosphine liberated upon ingestion of calcium phosphide. Thus, the generation of such data in a 90d-study in dogs is not likely to be of value for the extrapolation to man. As consequence, the conduct of such a study is not considered to be required, and should be avoided for animal welfare reasons.

4.7.1.7 Summary and discussion of repeated dose toxicity

In summary, a short-term NOAEL of 1.1 mg PH_3/kg bw/d, equivalent to 3.0 mg calcium phosphide/kg bw/d, was established. No specific classification/labelling are required.

4.7.1.8 Comparison with criteria of repeated dose toxicity findings relevant for classification according to DSD

There are no relevant data to compare with criteria.

4.7.1.9 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification according to DSD

No specific classification/labelling required.

4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

There is no evidence of specific target organ toxicity after repeated exposure of calcium phosphide.

4.8.1 Summary and discussion of repeated dose toxicity findings relevant for classification as STOT RE according to CLP Regulation

No toxicity to a specific organ in the absence of lethality was observed in repeated dose toxicity studies. There are no relevant data to discuss specific target organ toxicity after repeated exposure.

4.8.2 Comparison with criteria of repeated dose toxicity findings relevant for classification as STOT RE

There are no relevant data to compare with criteria.

4.8.3 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification as STOT RE

No specific classification/labelling required.

RAC evaluation of repeated dose toxicity (DSD) and specific target organ toxicity (CLP) – repeated exposure (STOT RE)
Summary of the Dossier submitter's proposal

[8] Okolie, N.P. et al. (2004): Phostoxin-induced biochemical and pathomorphological changes in rabbits. Indian J Exp Biol. 42 (11), 1096-9.

Oral: Two 90-day oral repeated dose toxicity studies are included in the CLH report. In one study (Muktha Bai et al., 2005) of unknown duration, zinc phosphide was given (presumably in the diet) at concentrations of 0, 50, 100, 200 and 500ppm. The NOEL was not determined and indicated to be below 50 ppm (3.5mg/kg bw/day). The observed effects were not described.

In the second oral 90-day gavage test (Schnellhardt et al., 1985), mortality was increased at 2 mg aluminium phosphide/kg bw/d (equivalent to 3.18 mg/kg bw/d tricalcium diphosphide, corresponding to 1.18 mg PH_3/kg bw/d) in both sexes, the NOAEL being 1 mg aluminium phosphide/kg bw/d, equivalent to 1.59 mg/kg bw/d tricalcium diphosphide corresponding to 0.59 mg PH_3/kg bw/d, respectively. However, these values are considered to be of limited reliability due to methodological deficiencies.

Neither of the reports provided data indicating any significant target organ toxicity at doses lower than those causing increased mortality.

Inhalation: In none of the two short-term (2-4 weeks) studies on rats nor in two subchronic (13 weeks) inhalation studies on rats were significant, adverse effects reported in internal organ at doses lower than those causing increased mortality.

Sensitivity of various mammal species to toxicity of metal phosphides is very similar as can be judged by very narrow range of median acute lethal doses. The level of repeated dose oral exposure to metal phosphide leading to increased mortality (e.g. - 3.18 mg/kg bw/d calcium phosphide are only slightly lower that median acute oral lethal doses (8.7mg/kg bw/d for aluminium phosphide or 11.2mg/kg bw/d of trimagnesium diphospide). The DS proposes no classification for repeated dose toxicity or specific target organ toxicity.

Comments received during public consultation

No comments were received during public consultation.

Assessment and comparison with the classification criteria

The RAC agreed with the DS that classification of tricalcium diphosphide for repeated dose toxicity (DSD) or specific target organ toxicity (STOT RE) is not warranted because of lack of specific target organ toxicity in the oral or inhalation short-term and 90-day studies in rats at doses not causing increased mortality. The interval between levels of lethal repeated dose oral or inhalation exposure to metal phosphides and median acute oral lethal doses or median lethal acute inhalation exposures is relatively small, suggesting that effects of acute and repeated exposure are mediated by the same mechanisms of PH_3 toxicity.

4.9 Germ cell mutagenicity (Mutagenicity)

4.9.1 Non-human information

Table 25: Summary table of relevant in vitro mutagenicity studies

Method	Test system (Organism, strain)	Concentra-tions tested	Results		Reference
			+ S9	- S9	

Method	Test system (Organism, strain)	Concentra-tions tested	Results		Reference
			+ S9	- S9	
Bacterial reverse mutation test (Ames test)	Salmonella typhimurium, TA98, TA100, TA1535, TA1537, TA1538, Escherichia coli WP2 Hcr-	0-25600 ppm (estimate)	Negative	Negative	Sutou, S. et al. (1982) (TOX2005-283)
Bacterial reverse mutation test (Ames test)	Salmonella typhimurium, TA98, TA100, TA102, TA1535, TA1537, TA1538	0-4340 ppm	Negative	Negative	Stankowski, L.F. (1990) (2001-685)
Bacterial reverse mutation test (Ames test)	Salmonella typhimurium, TA98, TA100, TA102, TA1537, TA1535	0-1780 ppm	Negative	Negative	Rajwani, L.S. (2000) (TOX2006-220)
Bacterial reverse mutation test (Ames test)	Salmonella typhimurium, TA98, TA100, TA102, TA1537, TA1535, E. coli WP2uvrA	Phosphine gas up to 1 %	Negative	Negative	Araki et al. (1994) (TOX2002-182)
Structural chromosome aberration	CHO-Kl-BH4 cells	0-4957 ppm	Equivocal	Equivocal	SanSebastian, J.R. (1990) (TOX2001-686)
Mammalian cell gene mutation (HGPRT test)	V79 hamster cells	0-6580 ppm	Negative	Negative	Leuschner, F. (1992) (TOX2005-284)

Table 26: Summary table of relevant in vivo mutagenicity studies

Method	Species, Strain, Sex, No/sex/group	Route and Frequency of application	Sampling times	Dose levels	Results	Reference
Chromosomal aberration test in mice	Swiss albino mice	Single oral (gavage)	1 day post exposure	0-1.5-3-6 mg/kg bw	Negative	Guna Sherlin, D.M. (1998) (TOX2006-222)
Micronucleus test in mice	Swiss albino mice	2 days, oral (gavage)	1 day after last exposure	0-1.5-3-6 mg/kg bw	Negative	Guna Sherlin, D.M. (1998) (TOX2006-221)
UDS test in rat primary hepatocytes	Rat, CDF (F344)/CrlBR, M, 10	Single whole body inhalation, 6 h exposure time	At 2 and 12-14 h, resp.	0-4.8-13-18-23 ppm	Negative	McKeon, M.E. (1993) (TOX2005-285)
Test for micronuclei	Mouse, Balb-c, M, F, 4-6	Whole body inhalation,2 weeks, 6 hours/day, 5 days/week	Not indicated	5.5+0.67 ppm	Negative	Barbosa, A. et al (1994) (TOX97-50676)
	M, F, 12	13 weeks, 6 hours/day, 5 days/week	Not indicated	0-0.3+0.1-1.0+0.2-4.5+0.8 ppm	Positive at the highest concentration	
Test for SCE, chromosome aberrations and micronuclei	Mouse, CD-1 (Charles River), M, 5	6 h inhalative exposure	At 20 hrs. post-exposure	0-5-10-15 ppm	Negative	Kligerman, A.D. et al. (1994) (TOX97-50677)
Test for SCE, chromosome aberrations and micronuclei	Mouse, CD-1 (Charles River), M, 3-5, Rat, F344/N (Charles River), M, 4-5	6 h/d inhalative exposure on 9 d during an 11 d period.	At 20 hrs. post-exposure	0-1.25-2.5-5 ppm	Negative	Kligerman, A.D. et al. (1994) (TOX2002-830)
Dominant lethal test	Mouse, B6C3F1 (Charles River), M, 50 (control: 30)	6 h/d inhalative exposure on 10 d during a 12 d period.	-	0-5 ppm		
Test for chromosome aberrations and micronuclei	Mouse (inbred swiss), 4	Zink phosphide, chromosome aberration test: acute: i.p., p.o. and s.c. Subacute: i.p., 5 days Micronucleus test: 2 x i.p. Sperm abnormality test: i.p., 5 days	24 h post exposure 6 h after last injection 35 days after first injection	20-20-40 mg/kg bw 8 mg/kg bw/d 20-30-40 mg/kg bw 20-30-40 mg/kg bw	Equivocal, however, study is not acceptable	Pal, B.B., Bhunya, S.P. (1995) (TOX2002-183
Dominant lethal test	Mouse, Swiss albino, control: 10 M, treated group: 11 M	Aluminium phosphide in peanut oil	-	0-6 mg/kg bw/day	Positive at toxic concentration	Rajesh Sundar, S. (1999) (TOX2006-224)

4.9.1.1 In vitro data

All submitted in vitro bacterial reverse mutation tests (Table 18) showed negative results. No clear result was obtained for the potential of PH_3 to cause clastogenic effects in CHO cells in vitro. The ability of the test design to detect potential clastogenic effects caused by PH_3 could not be demonstrated convincingly.

4.9.1.2 In vivo data

6 submitted in vivo tests (Table 19) showed negative results. In a subchronic (13 weeks, mice) in vivo test the formation of micronuclei was increased at the highest test concentration (approaching the LD_{50}). However, such exposure conditions are unlikely to be encountered in an occupational environment. In a dominant-lethal-test in mice with aluminium phosphide in peanut oil the post implantation loss was increased and the number of live implants was reduced. At the only dose level also toxic effects have been observed. However, the quality of the study was limited. An inhalative dominant-lethal test in mice was negative.

4.9.2 Human information

An increased rate of chromosomal aberrations has been reported after exposure to phosphine in fumigators Gary et al., 1989). However, it was not possible to assess exact exposure conditions from this publication. Furthermore, it was not clear, whether other possible confounding factors (e.g. smoking, age) were adequately considered in this study. Although the human evidence presented was contradictive and inconclusive, the overall weight of evidence suggested clearly that calcium phosphide had no genotoxic potential.

4.9.3 Other relevant information

No other relevant information is available.

4.9.4 Summary and discussion of mutagenicity

Overall, calcium phosphide/PH_3 is not likely to be genotoxic in humans on relevant exposure conditions.

4.9.5 Comparison with criteria

There are no relevant data to compare with criteria.

4.9.6 Conclusions on classification and labelling

No specific classification/labelling required.

RAC evaluation of germ cell mutagenicity
Summary of the Dossier submitter's proposal All in vitro bacterial reverse mutation tests presented in the CLH dossier show negative results. No clear potential of PH_3 to cause clastogenic effects in CHO cells could be demonstrated in vitro and the discrimination power of the test design was not convincing. Moreover, relevant in vivo tests show negative results. On the basis of these

observations, the DS does not consider tricalcium diphosphide as likely to be genotoxic in humans under relevant exposure conditions.

Comments received during public consultation
No comments were received during public consultation.

Assessment and comparison with the classification criteria

An increased rate of chromosomal aberration has been reported after exposure to phosphine in humans – in fumigators (Gary et al., 1989). However, it is not possible to assess the exact exposure conditions nor is it clear whether other possible confounding factors (e.g. smoking, age) were adequately considered in this study. All submitted in vitro bacterial reverse mutation tests with phosphine gas up to 25600 ppm concentration showed negative results. The same conclusion can be drawn regarding mammalian cell gene mutation test in V79 hamster cells. No clear result was obtained for the potential of PH_3 to cause clastogenic effects in Chinese hamster ovary cells (CHO-Kl-BH4) in vitro.

With regard to in vivo tests, a number of chromosomal aberrations and micronucleus tests in mice as well as the unscheduled DNA synthesis (UDS) assay in rat primary hepatocytes gave negative results using differing exposure routes - oral gavage (up to 6 mg/kg bw) and inhalation (up to 15 ppm in 6 hours inhalative exposure and up to 5 ppm in prolonged repeated inhalative exposure). In a subchronic (13 weeks, mice) in vivo test (Barbosa, A. et al, 1994) the formation of micronuclei was increased at the highest test concentration approaching the LD_{50} (4.5+0.8 ppm). In a dominant-lethal-test in mice with aluminium phosphide in peanut oil (Rajesh Sundar, 1999) the post implantation loss was increased and the number of live implants was reduced at toxic concentration (6 mg/kg bw/day - only dose level applied). But DS indicates that the quality of the study was limited. The overall weight of evidence suggests that tricalcium diphosphide has no genotoxic potential in vivo.

The RAC agreed with the DS that classification of tricalcium diphosphide as a germ cell mutagen is not warranted.

4.10 Carcinogenicity

Table 27: Summary table of relevant carcinogenicity studies

Study and dose levels (mg/kg/day)	NO(A)EL	LOEL	Reference
Combined rat chronic (2 year) toxicity and carcinogenicity study, 0, 0.3, 1, and 3 ppm by inhalation with purified PH_3	Toxicity: NOAEL: 3 ppm phosphine equivalent to 0.0042 mg/L or 1.1 mg/kg bw/day	Toxicity: LOEL: > 3 ppm Based on lack of systemic toxicity at any dose level	Newton, 1998 (TOX2000-98)
	Carcinogenicity: NOEL: 3 ppm	Carcinogenicity: LOEL: > 3 ppm based on lack of carcinogenicity at any dose level	
Rat chronic (2 year) toxicity, oral, levels of phosphine in diet after fumigation ranged from 0.167-7.5 mg/kg	No effects observed. However, the study is considered to be not acceptable.	-	Hackenberg, 1972/1969 (TOX96-52058) / (TOX2005-286)
Rat chronic (2 year) toxicity, oral, level of phosphine in diet after fumigation 5 ppb	No effects observed. However, the study is considered to be not acceptable.	-	Telle et al., 1985 (TOX2002-831)

4.10.1 Non-human information

4.10.1.1 Carcinogenicity: oral

In two limited dietary studies, rats received diets treated with phosphine released from aluminium phosphide. Behaviour, general appearance, survival, body weight, food consumption, haematology, blood chemistry, urine analyses and bone smear data, as well as gross and microscopic findings and rate of tumour development, did not reveal any toxic effects from the aluminium phosphide treated diet. However, the test design of both studies was insufficient. Therefore, the oral studies are considered to be not acceptable.

4.10.1.2 Carcinogenicity: inhalation

Phosphine was assessed for chronic inhalation toxicity and carcinogenicity in a combined 104 week study in rats. In the inhalation study, body weight, food consumption, routine haematology, serum biochemical, and urinary analyses were all comparable to control animals. Ophthalmological observations, gross pathology, organ weights and histopathology indicated no adverse effects from phosphine exposures. The NOAEL was 1.1 mg/kg bw/day (equivalent to 3.0 ppm), the highest concentration tested.

4.10.1.3 Carcinogenicity: dermal

No data available.

4.10.2 Human information

No data available.

4.10.3 Other relevant information

Based on lack of exposure and the absence of genotoxic concern waiving of a long term/ carcinogenicity study in a second species was seen as justified.

4.10.4 Summary and discussion of carcinogenicity

In conclusion, there were no treatment related changes suggestive of a toxic or carcinogenic effect seen in rats following 52 weeks and 2 years of whole-body inhalation exposure to 0.3, 1 or 3 ppm phosphine. The NOAEL was 1.1 mg/kg bw/day (equivalent to.3.0 ppm) the highest concentration tested.

4.10.5 Comparison with criteria

There are no relevant data to compare with criteria.

4.10.6 Conclusions on classification and labelling

No specific classification/labelling required.

RAC evaluation of carcinogenicity

Summary of the Dossier submitter's proposal

There are no carcinogenicity studies conducted with tricalcium diphosphide reported in the CLH report. One two-year combined toxicity-carcinogenicity rat inhalation study conducted with phoshine gas is reported. Additionally, two two-year oral rat feeding studies where feed was fumigated with phoshpine gas are included but were not considered acceptable.

There were no treatment related changes suggestive of a toxic or carcinogenic effect seen in rats following 52 weeks and 2 years of whole-body inhalation exposure to 0.3, 1 or 3 ppm phosphine. The NOAEL is 1.1 mg/kg bw/day (equivalent to 3.0 ppm), the highest concentration tested. According to these results, the DS concludes that no classification is required for carcinogenicity.

Comments received during public consultation

No comments were received during public consultation.

Assessment and comparison with the classification criteria

No specific animal studies on carcinogenicity conducted with tricalcium diphosphide were provided by the DS. Human data are lacking as well.

In two 2-year dietary studies provided by the DS, rats received diets fumigated with phosphine released from aluminium phosphide. The concentrations in the food ranged from 0.167 to 7.5 mg/kg in one case (Hackenberg, 1972/1969) and ~5 ppb in other case (Telle et al., 1985). Behaviour, general appearance, survival, body weight, food consumption, haematology, blood chemistry, urine analyses and bone smear data, as well as gross and microscopic findings and rate of tumour development, did not reveal any toxic effects. However, these studies are not considered acceptable due to poor selection and reporting of the phosphine doses applied.

A combined 2 year rat chronic toxicity and carcinogenicity study by inhalation using 0, 0.3, 1, and 3 ppm purified phosphine gas is also reported (Newton, 1998). Body weight,

food consumption, routine haematology, serum biochemical, and urinary analyses were all comparable to control animals. Ophthalmological observations, gross pathology, organ weights and histopathology indicated no adverse effects from phosphine exposures as well as no formation of neoplasms. The estimated NOAEL is 3 ppm phosphine equivalent to 0.0042 mg/l or 1.1 mg/kg bw/day (the highest concentration used; it should be mentioned that recalculated LC_{50} for tricalcium diphosphide concerning acute exposure is 0.04 mg/l obtained by Waritz, and Brown, 1975). Accordingly, the LOEL is > 3 ppm or >1.1 mg/kg bw/day.

Taking into account that no formation of neoplasms was observed as well as that tricalcium diphosphide can not be considered a germ cell mutagen, the RAC agreed that classification for carcinogenicity is not warranted. In addition, the RAC took into account that phosphine is not classified as carcinogenic in the CLP.

4.11 Toxicity for reproduction

Table 28: Summary table of relevant reproductive toxicity studies with phosphine

Study and dose levels (mg/kg/day)	NO(A)EL	LOEL	Reference
Rat 2-generation study with fumigated diet	No effects in result of fumigation. Concentration of as in diet not measured. The study is not acceptable	No effects in result of fumigation. Concentration of as in diet not measured.	Cabrol, 1986 (TOX2005-189)
Rat developmental toxicity 0, 0.03, 0.3, 3.0, 5.0 and 7.5 ppm (by inhalation)	Maternal toxicity: NOEL: 5 ppm	Maternal toxicity: LOEL: 7.5 ppm Based on mortality	Schroeder, 1989 (TOX2001-687)
	Developmental toxicity: NOEL: 5 ppm *) Equivalent to 0.007 mg/L air or 1.9 mg/kg bw/day	Developmental toxicity: LOEL: > 5 ppm Up to 5 ppm no developmental tox. was observed, dose group 7.5 ppm was early terminated	

*) = The analytical concentration was 4.9 ppm.

4.11.1 Effects on fertility

4.11.1.1 Non-human information

No acceptable data available

4.11.1.2 Human information

No data available

4.11.2 Developmental toxicity

4.11.2.1 Non-human information

The inhalative (whole body) developmental toxicity study in rats revealed no specific developmental effects and the NOAEL of 1.9 mg/kg bw/d phosphine (equivalent to 4.9 ppm) was set based on mortality occurring in dams.

4.11.2.2 Human information

No data available.

4.11.3 Other relevant information

Neither an acceptable two-generation study in rats nor a developmental study in rabbits has been submitted. Based on the assumptions that lethality would be the main endpoint, that maternal toxicity would dominate any specific effects, and that no species specific differences were anticipated, the experts at PRAPeR meeting agreed that neither a two-generation study nor a developmental study with rabbits was necessary for a satisfactory evaluation of the active substance.

4.11.4 Summary and discussion of reproductive toxicity

Specific adverse effects on reproduction (fertility/development) related to exposure towards calcium phosphide are not considered likely based on the results of an inhalative teratogenicity study in rats as well as on the general toxicological profile of the metal phosphides.

4.11.5 Comparison with criteria

There are no relevant data to compare with criteria.

4.11.6 Conclusions on classification and labelling

Classification/labelling for reproductive or developmental toxicity not required.

RAC evaluation of reproductive toxicity
Summary of the Dossier submitter's proposal No specific studies on reproductive toxicity conducted with tricalcium diphosphide were reported in the CLH report. The DS does not consider specific adverse effects on reproduction (fertility/development) related to exposure to tricalcium diphosphide likely to occur, based on the results of an inhalation teratogenicity study in rats conducted with phosphine gas, as well as on the general toxicological profile of the metal phosphides. **Comments received during public consultation** No comments were received during public consultation. **Assessment and comparison with the classification criteria** No specific studies on reproductive toxicity conducted with tricalcium diphosphide are provided by the DS. Human data are lacking as well. No acceptable information with respect to fertility are given in the CLH report as the rat 2-generation study with phosphine fumigated diet (Cabrol, 1986) showing no effects is of poor quality – the concentration of phosphine in the food was not measured. With respect to developmental toxicity, a whole body inhalation developmental toxicity study in rats using 0, 0.03, 0.3, 3.0, 5.0 and 7.5 ppm of phosphine has been carried out

(Schroeder, 1989). No developmental toxicity was observed up to 5 ppm – the estimated $NOAEL_{developmental}$ is 4.9 ppm equivalent to 0.007 mg/l or 1.9 mg/kg bw/d phosphine. The same value is set for $NOAEL_{maternal}$. It should be mentioned that recalculated LC_{50} for tricalcium diphosphide concerning acute exposure is 0.04 mg/l obtained by Waritz and Brown (1975). The LOAEL for maternal toxicity is 7.5 ppm but for developmental effects > 5 ppm based on mortality occurring in dams.

The RAC agreed with the conclusions drawn by the DS that lethality would be the main endpoint for phosphine and maternal toxicity would dominate any specific effects. Therefore, classification for reproductive toxicity is not warranted. The RAC took into account that phosphine is not classified as reproductive toxicant under CLP.

4.12 Other effects

4.12.1 Non-human information

4.12.1.1 Neurotoxicity

The neurotoxicity of phosphine has been assessed in rats in an acute and a 90-day inhalation study. In the acute neurotoxicity study, rats were exposed to 0, 20, 30 and 40 ppm phosphine gas (nominal conc.) administered via whole body inhalation exposure for one session of four hours duration. The NOAEL of phosphine in rats was 40 ppm (analytical conc. 38 ppm) with regard to anatomic pathology and the behavioural and neurological status observed in the functional observational battery, and less than 20 ppm with regard to changes in motor activity on day 1. In the subchronic neurotoxicity study, rats were exposed to phosphine via whole body exposure at levels of 0.3, 1 and 3 ppm, 6 hours per day, 5 days per week, for 13 weeks. Due to equivocal effects seen in high dose males, and the lack of effects seen in females the NOAEL of phosphine for systemic/neurotoxic effects in rats exposed over a 90-day period is 3 ppm, the highest dose tested in this study.

4.12.1.2 Immunotoxicity

No data available.

4.12.1.3 Specific investigations: other studies

It was demonstrated that phosphine or other phosphide derived reaction products induced Heinz body formation in relatively low concentrations (1.25 ppm) in normal human erythrocytes. The time course for the induction of Heinz bodies is relatively slow (4 h). The formation of Heinz bodies by phosphine is oxygen-dependent, consistent with earlier work regarding the insecticidal properties of the chemical. Finally, these in vitro data lead to the speculation that prolonged in vivo exposure to phosphine in concentrations exceeding the PEL might have an adverse effect on haemoglobin in susceptible segments of the worker population exposed to the chemical.

The results of another study show that after acute poisoning of rats by phosphine the respiration of the isolated liver mitochondria is diminished. The oxidation of α-ketoglutarat turned out to the most sensitive parameter. The oxidative phosphorylation, however, remains on a normal level. In general, the disturbance equals that of phosphine action on isolated mitochondria in vitro. Similar effects have been observed on the isolated sarcosomes of heartmuscle of poisoned animals on an early state of intoxication. But in the sarcosome respiration and phosphorylation is uncoupled at the same time. Since the respiration of Neurospora crassa is also decreased by phosphine it is to assume that this

agent acts by this mechanism on living cells in general. The same kind of disturbance can be demonstrated in the mitochondria after chronic administration of doses which are far below the toxic ones of phosphine and by which animals do not show any sign of damage. There is a small but considerable fall of CoA in the liver of acute poisoned animals.

4.12.1.4 Human information

Among the examined persons, occupied in the production of Polytanol (Calcium phosphide), no health impairment was detected over a period of 3 to 16 years. The case reports are considered to be representative of the numerous records of poisoning cases, mainly in connection with suicide, but also with accidental poisoning a.o. of children in developing countries. Diagnosis is mainly based on the history of intake, gastrointestinal symptoms, shock symptoms and silver nitrate impregnated paper test. Main symptoms are severe circulatory, cardiac, and renal failure, uraemia, hepatic damage, changes in ECG, and respiratory distress connected with a high mortality rate. Histopathological changes have mainly been observed in lungs, liver, heart and kidney. Since an antidote is not available, therapy relies on treatment of the clinical symptoms and administration of high doses of corticoids.

4.12.2 Summary and discussion

There are no other relevant effects.

4.12.3 Comparison with criteria

There are no relevant data to compare with criteria.

4.12.4 Conclusions on classification and labelling

There are no other relevant effects to compare with criteria for classification and labelling.

5 ENVIRONMENTAL HAZARD ASSESSMENT

Not relevant for this dossier. There is no need for an amendment of the current environmental classification.

6 ANNEXES

A confidential annex is enclosed in the technical dossier.