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**

Contact details for dossier submitter:

BAuA
Federal Institute for Occupational Safety and Health
Federal Office for Chemicals
Friedrich-Henkel-Weg 1-25
D-44149 Dortmund, Germany

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

Date: **May 2012**

CONTENTS

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 $C \geq 0.25\%$ 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:

-

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

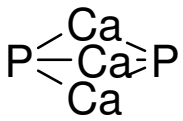
1 IDENTITY OF THE SUBSTANCE

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.

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.

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. OECD 404	Rabbit, New Zealand White 3M	Zinc phosphide 0.5 g/animal	Not irritating	None	Brunt, P. (2001) (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.

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.

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]).

---

[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.

- 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 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.

---

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

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

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

No specific classification/labelling required.

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	
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.

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.

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.

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.