Committee for Risk Assessment

RAC

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/F

Adopted
7 March 2013

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CLH-O-0000003602-81-01/F

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

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

Chemical name: tricalcium diphosphide

EC number: 215-142-0

CAS number: 1305-99-3

The proposal was submitted by **Germany** and received by the RAC on **21/06/2012.**

In this opinion, all classifications are given firstly in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS) and secondly, according to the notation of 67/548/EEC, the Dangerous Substances Directive (DSD).

PROCESS FOR ADOPTION OF THE OPINION

The **Netherlands** has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation*** on **21/06/2012.** Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **6/08/2012**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by the RAC: **Normunds Kadikis.**

Co-rapporteur, appointed by the RAC: **Boguslaw Baranski**

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

The RAC opinion on the proposed harmonised classification and labelling was reached on **7 March 2013** and the comments received are compiled in Annex 2.

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

OPINION OF THE RAC

The RAC adopted the opinion that **tricalcium diphosphide** should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	**Hazard statement Code(s)**	**Pictogram, Signal Word Code(s)**	**Hazard state-ment Code(s)**	**Suppl. Hazard statement Code(s)**		
Current Annex VI entry	015-003-00-2	calcium phosphide; tricalcium diphosphide	215-142-0	1305-99-3	Water-react. 1 Acute Tox. 2* Aquatic Acute 1	H260 H300 H400	GHS02 GHS06 GHS09 Dgr	H260 H300 H400	EUH029	M = 100	
Dossier submitter's proposal	015-003-00-2	calcium phosphide; tricalcium diphosphide	215-142-0	1305-99-3	**Modify:** Acute Tox. 2 **Add:** Acute Tox. 3 Skin Corr. 1A	H300 **Add:** H311 H314	GHS06 **Add:** GHS05	H300 **Add:** H311 H314			
RAC opinion	015-003-00-2	calcium phosphide; tricalcium diphosphide	215-142-0	1305-99-3	**Modify:** Acute Tox. 2 **Add:** Acute Tox. 3 Acute Tox. 1 Eye Dam. 1	H300 **Add:** H311 H330 H318	GHS06 **Add:** GHS05	H300 **Add:** H311 H330 H318	**Add:** EUH032		
Resulting Annex VI entry if agreed by COM	015-003-00-2	calcium phosphide; tricalcium diphosphide	215-142-0	1305-99-3	Water-react. 1 Acute Tox. 2 Acute Tox. 3 Acute Tox. 1 Eye Dam. 1 Aquatic Acute 1	H260 H300 H311 H330 H318 H400	GHS02 GHS06 GHS05 GHS09 Dgr	H260 H300 H311 H330 H318 H400	EUH029 EUH032	M = 100	

Classification and labelling in accordance with the criteria of Directive 67/548/EEC

	Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
Current Annex VI entry	015-003-00-2	calcium phosphide; tricalcium diphosphide	215-142-0	1305-99-3	F; R15/29 T^+; R28 N; R50	F; T^+; N R: 15/29-28-50 S: (1/2-)22-28-36/37/-43-45-61	N; R50: C ≥ 0,25%	
Dossier submitter's proposal	015-003-00-2	calcium phosphide; tricalcium diphosphide	215-142-0	1305-99-3	**Add:** Xn; R21 C; R35	**Add:** C R: 21-35 S: 3/9/14/49-8-26-30/39-60		
RAC opinion	015-003-00-2	calcium phosphide; tricalcium diphosphide	215-142-0	1305-99-3	**Add:** T^+; R26 Xn; R21 R32 Xi; R38-41	**Add**: R: 21-26-32-38-41 S: 3/9/14/49-8-26-30/39-60		
Resulting Annex VI entry if agreed by COM	015-003-00-2	calcium phosphide; tricalcium diphosphide	215-142-0	1305-99-3	F; R15/29 T^+; R26/28 Xn; R21 Xi; R38-41 R32 N; R50	F; T^+; N R: 15/29-21-26/28-32-38-41-50 S:(1/2)-3/9/14/49-22-26-30-36/37/39-43-45-60-61	N; R50: C ≥ 0,25%	

SCIENTIFIC GROUNDS FOR THE OPINION

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.

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.

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.

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.

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).

RAC evaluation of repeated dose toxicity (DSD) and specific target organ toxicity (CLP) – repeated exposure (STOT RE)

Summary of the Dossier submitter's proposal
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/day (equivalent to 3.18 mg/kg bw/day tricalcium diphosphide, corresponding to 1.18 mg PH_3/kg bw/day) in both sexes, the NOAEL being 1 mg aluminium phosphide/kg bw/day, equivalent to 1.59 mg/kg bw/day tricalcium diphosphide corresponding to

0.59 mg PH_3/kg bw/day, 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/day calcium phosphide are only slightly lower that median acute oral lethal doses (8.7mg/kg bw/day for aluminium phosphide or 11.2mg/kg bw/day 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.

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-KI-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.

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.

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.

References

Roy, B.C. (1998) Acute inhalation toxicity of aluminium phosphide technical in rats. TOX2006-215, unpublished.

Waritz, R.S. and Brown, R.M. (1975) Acute and subacute inhalation toxicities of phosphine, phenylphosphine and triphenylphosphine. Am. Ind. Hyg. Assoc., 36, 1975, 452-458 TOX2002-176

ANNEXES:

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

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