Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Phosmet (ISO); *S*-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl] *O,O*-dimethyl phosphorodithioate

EC Number: 211-987-4

CAS Number: 732-11-6

CLH-O-0000001412-86-113/F

Adopted

3 June 2016

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON PHOSMET (ISO); *S*-[(1,3-DIOXO-1,3-DIHYDRO-2*H*-ISOINDOL-2-YL)METHYL] *O,O*-DIMETHYL PHOSPHORODITHIOATE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: **Phosmet (ISO); *S*-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl] *O,O*-dimethyl phosphorodithioate**
EC number: **211-987-4**
CAS number: **732-11-6**
Dossier Submitter: **Spain**

GENERAL COMMENTS

Date	Country	Organisation		Type of Organisation	Comment number
13.11.2015	France			MemberState	1
	Comment received				
	MSCA-FR agrees with the classification proposal				
	Dossier Submitter's Response				
	Thank you for your agreement with our proposal				
	RAC's response				
	Thank you.				

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Germany		MemberState	2
Comment received				
The German CA supports the proposed classification.				
Dossier Submitter's Response				
Thank for agreeing				
RAC's response				
Thank you.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Germany		MemberState	3

Comment received

For the assessment of carcinogenicity two chronic toxicity/oncogenicity studies are available. One in rats and one in mice. Both were within similar dose ranges and no evidence for carcinogenicity was found in the rat study.
In the chronic toxicity/oncogenicity study in B6C3F1 mice (Katz et al. 1984) significant increased incidences (45%) of hepatocellular adenoma were reported in top dose males. According to the Guidance on the Application of CLP Criteria liver is a tissue that is known to have a high spontaneous incidence of tumours in B6C3F1 mice. However, the incidence was around twice as high as in concurrent controls (22%) and outside historical controls (42%) from a study that was conducted in the same laboratory 2 years later (Katz et al. 1986-Addendum I). The incidence was within historical controls presented by Haseman et al. 1999 (29%, range 4-60%). The latter, however, covered a range of 25 years and around 400 studies and was dismissed by the EFSA Peer Review in 2006 due to high variability.
In the Guidance to the Application of the CLP Criteria one requirement for application of historical control data is contemporaneousness, i.e. within a period of up to around 5 years of the relevant study. Therefore contemporary studies compiled by Haseman et al. 1984 (data from 51 studies covering the years 1981 to 1984; hepatocellular adenoma incidence in male B6C3F1 mice: 10,3 ± 5,5%) that fulfil this requirement are considered more relevant for discussion in the CLH report than the dismissed Haseman et al. 1999 data. When considering only the reported historical control data of Katz et al. 1986 and the data of Haseman et al. 1984, liver adenomas still occur spontaneously with a high variability in male B6C3F1 mice.
Additionally, while in the CLH report it was stated that a slight but significant body weight increase in male B6C3F1 mice in top dose group of 8% was not considered biologically significant, data from Haseman et al. 1998 show that even small increases in bodyweight increase the incidence of hepatocellular adenoma in untreated male B6C3F1 mice and may add to the weight

In summary, the presented study in B6C3F1 mice does not raise sufficient evidence for carcinogenic properties of phosmet. This would be in line with the ECB TC C&L that did not agree to classify phosmet for carcinogenicity and the EFSA Peer Review of phosmet (EFSA, 2011) that did not include a proposal of classification regarding the carcinogenic potential of this substance but mentioned that "the experts could not agree on the proposed classification as carcinogenic with the application of R40."

Further comments on carcinogenicity:

Page 92/93: Please clarify/correct: In table 44 the data are related to a number of tumours in 50 animals, in table 46 the same data are related to 60 animals.

Page 92: Please highlight with "**" in table 44 the significant increase of hepatocellular adenomas in male B6C3F1 mice at 100 ppm.

Literature:
Haseman, J.K., Huff, J., Boorman, G.A. (1984) "Use of historical control data in carcinogenicity studies in rodents" Toxicology Pathology, Volume 12, Issue 2, pp. 126-135.

Haseman, J.K., Hailey, J.R., Morris, R.W (1998) "Spontaneus neoplasm incidences in Fischer 344 rats and B6F3C1 mice in two-year carcinogenicity studies: A national toxicology program update" Toxicologic Pathology, Volume 26, Issue 3, pp. 428-441.

Dossier Submitter's Response

Thanks for supporting the Spanish proposal of not classification regarding carcinogenicity. The increase in the incidence of hepatocellular adenoma in high dosed mice observed is of questionable biological significance since the B6C3F1 strain of mouse has been well established as sensitive to liver tumour induction. The Guidance on the Application on the CLP Criteria (ECHA, June 2015) has reported that liver tumours in B6C3F1 mice is one of the examples of animal tissues with a high spontaneous tumour incidence and a cautious view of these kind of tumours have to be done. After a detailed review of the available data (the B6C3F1 strain of mouse has been well stablished as sensitive to liver tumour induction, no other tumour type was detected in mice and no increases in liver tumours were seen in exposed rats; a genotoxicity/ mutagenicity database which shows that phosmet is neither genotoxic nor mutagenic in vivo) the liver tumour findings would not in themselves justify classification of phosmet.

On regards to further comments on carcinogenicity, the table 44 is added rectified:

Table 44: Selected incidences of microscopic effects after 12 months (interim sacrifice) + after 24 months (terminal sacrifice) – Neoplastic findings

	0 ppm	**5 ppm**	**25 ppm**	**100 ppm**
	No. of mice affected/No. of mice examined			
Males:				
Liver				
Hepatocellular adenoma	13/60	10/60	14/60	27/60**
Adenocarcinoma	-/60	-/60	-/60	1/60
Hepatocellular carcinoma	13/60	11/60	11/60	14/60
Lymphoma	1/60	-/60	2/60	-/60
Hemangiosarcoma	-/60	-/60	5/60	1/60
Reticulum cell sarcoma	1/60	3/60	1/60	-/60
Sarcoma	-/60	1/60	-/60	1/60
Females:				
Liver				
Hepatocellular adenoma	6/60	4/60	5/59	11/60
Hepatocellular carcinoma	5/60	4/60	3/59	9/60
Lymphoma	6/60	6/60	7/59	6/60
Strom cell sarcoma	-/60	-/60	-/59	1/60
Hemangio sarcoma	-/60	-/60	2/59	-/60
Fibrosarcoma	-/60	1/60	-/59	-/60
Males				
Harderian gland				
Adenoma	3/60	7/60	4/59	9/60
Lymphoma	-/60	-/60	1/59	-/60
Adenocarcinoma	-/60	2/60	-/59	-/60
Females				
Harderian gland				
Adenoma	1/59	-/15	3/14	2/59
Adenoma, papillary cyst	1/59	-/15	-/14	-/59
Adenocarcinoma	-/59	1/15	-/14	1/59
Lymphoma	1/59	-/15	2/14	3/59

Statistics: According to study authors, hepatic tumors were analysed with a level of significance of $p < 0.01$ and stated that hepatic adenomas were significantly increased in males at 100 ppm. **Significantly different from the 0 ppm dose level, $p < 0.01$
RAC's response
Thank you for valuable comments and corrections. RAC agrees not to classify phosmet for carcinogenicity.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Germany		MemberState	4
Comment received				
Based on several findings phosmet has clear genotoxic properties in bacterial and mammalian cell assays in vitro. In vivo four acceptable and one additional study were negative. One in vivo study, classified as not acceptable due to lack of information, showed a significant not dose-related increase of chromosomal aberrations in bone marrow cells of white non-linear mice. Considering the positive in vitro and negative in vivo data the question is raised if the substance was able to reach the bone marrow. On page 64 of the CLH report is stated: "It should be noted that phosmet reaches bone marrow […] according to toxicokinetics data", while according to the distribution data of the toxicokinetics section (p. 17) "…the tissues contained low levels of radioactivity (≤ 1 % of the administered dose) in all dose groups", „… and lowest activity in the fat and bone." Please clarify. Furthermore, the statement in the summary to the in vivo DNA alkylation assay (Dedek et al. 1984; ip administration, vehicle: propylene glycol) „Phosmet has a limited solubility in water and possibly due to this fact it cannot penetrate the target site of DNA bases" is mistakable. Please discuss/clarify the impact of this information regarding the outcomes of the other in vivo assays. Considering the presented study results, under assumption that the substance reached the bone marrow to a reasonable extent, we support the proposal not to classify for mutagenicity.				
Dossier Submitter's Response				
Thank you for your agreement with our proposal of not classification on genotoxicity The available data do not provide sufficient evidence for classificantion. Based on the results of all studies provided, the weight of evidence suggests no in vivo genotoxic potential for phosmet. Therefore, phosmet does not warrant classification for mutagenicity according to CLP criteria.				

RAC's response
RAC agrees with German MSCA comment that it is not clear in which way phosmet toxicokinetic data support the statement "It should be noted that phosmet reaches bone marrow […] according to toxicokinetics data". Namely, only information on phosmet distribution in tissues at 96 h after dosing are available, as an evidence against accumulation of Phosmet in tissues (from revised DAR: "Distribution showed that very little radioactivity was detected in any individual tissues at 96 h after dosing. The highest levels were in the whole blood and the lowest ones in bone and fat. No evidence of accumulation was found."). Data on phosmet distribution early after treatment are not available to RAC. However, RAC is of the opinion that phosmet distribution to bone marrow is not an issue. Bone marrow is a well perfused tissue, and chemical presents in the blood is expected to be accessible to the bone marrow as well (ECHA Guidance on the Biocidal Products Regulation, Volume III Human Health - Part B Risk Assessment, Version 2.0 October 2015). Toxicokinetic data in CLH report showed systemic availability of phosmet after oral exposure. Oral absorption in rats was shown to be fast and almost complete (based on urinary excretion of 75% to 89% at 96h after dosing, cage wash radioactivity recovery and radioactivity recovery in tissues, Fisher 1989), and wide distribution in tissues was observed (Ford 1964). In addition, as pointed out in CLH report, small decrease of % of PCEs among total erythrocytes at 24h was observed (11% in males, 6% in females) at single oral dose applied in micronucleus test, suggesting phosmet-induced bone marrow toxicity. RAC also agrees with German MSCA comment regarding the DS statement that low water solubility on phosmet's could decrease its DNA alkylating ability (i.e. its ability to reach DNA binding sites; *in vivo* DNA alkylation assay by Dedek *et al.* 1984). The relationship between water solubility and alkylating property of a substance seems not to be straightforward, as shown by Wolfe *et al.* 2013. Namely, the authors showed that by increasing hydrophilicity of derivatives of duocarmycin SA, potent antitumour compound, a decrease in cell growth inhibitory activity and DNA alkylation efficiency was found, supporting the dominance of the hydrophobic interactions in stabilizing non-covalent complex of this compound with DNA (so called "hydrophobic binding-driven bonding") Wolfe AL, Duncan KK, Lajiness JP, Zhu K, Duerfeldt AS, Boger DL. A fundamental relationship between hydrophobic properties and biological activity for the duocarmycin class of DNA-alkylating antitumor drugs: hydrophobic-binding-driven bonding. J Med Chem 2013;56:6845-57).

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Sweden		MemberState	5
Comment received				
No experimental values are indicated for any of the studies referred to (neither in the summary table of relevant studies, nor in the text). It is therefore not possible for the reader of the CLH report to evaluate the results on mutagenicity other than by taking general statements about an observed effect or no observed effect into account. The substance is considered to be positive in all available in vitro gene mutation studies (4 in bacteria, 1 in mammalian cells and 1 in yeast). Two in vivo UDS studies are available as follow-up studies of the induction of gene mutations observed in vitro. The in vivo UDS studies were negative, but it can be questioned if the test substance reached the target				

cells in sufficient amount to induce a detectable possible genotoxic effect. However, we agree that the available results do not support that the substance should be classified for germ cell mutagenicity.

Dossier Submitter's Response

Thanks for supporting not classification regarding genotoxicity.

Phosmet is genotoxic in vitro based on the positive responses observed in the Salmonella test and in an in vitro mammalian gene mutation assay. The only in vivo study that was positive was reported by Kurinnyi (1975) in a bone marrow in mice. However, the increase in chromosome aberrations observed was not dose-dependent and the study was not considered acceptable. Besides, the results in one in vitro chromosome aberration assay and in two in vivo micronucleus tests were negative. Furthermore, negative results were reported in two vivo UDS studies and in a DNA alkylation assay.

Highly relevant is the most recent in vivo UDS study (Proudlock R.J., 1998), acceptable and of known purity, where toxicological signs were observed at all groups at 2h, and at 14 h at 108 and 108 and 180 mg/kg bw.

The available data do not provide sufficient evidence for classificantion. Based on the results of all studies provided, the weight of evidence suggests no in vivo genotoxic potential for phosmet. Therefore, phosmet does not warrant classification for mutagenicity according to CLP criteria.

RAC's response

Thank you for the comment. RAC also agrees with no classification for genotoxicity, and some additional clarifications regarding genotoxicity studies shown in CLH report are presented in ODD.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Germany		MemberState	6

Comment received

Based on the data presented, we support not to classify phosmet for reproductive toxicity. This would be in line with the ECB TC C&L that agreed not to classify phosmet for reproductive toxicity.

Dossier Submitter's Response

Thanks for supporting not classification regarding reproductive toxicity.

RAC's response

RAC agrees not to classify phosmet for developmental toxicity.
Nevertheless, classification for fertility is proposed (Repr. 2, H361f) based on reduced mating index, fertility index and gestation index at 80 ppm and 300 ppm in both generations and at both matings, generally in a dose-dependent manner, in 2-generation study in rats. Namely, although parental toxicity was noted at 300 ppm, and, to a certain degree, also at 80 ppm dose level, RAC does not consider it serious enough to explain fertility adverse effects solely as a consequence of general toxicity of phosmet. Available data for phosmet does not allow determination of mechanisms responsible for observed changes in fertility indices and an assessment of their relevance for humans. Although treatment-related morphological changes in reproductive organs, including spermatogenesis, were not found, there is a possibility that observed fertility effects are caused by changed rats' behaviour as a consequence of neurotoxic effects of phosmet, or

via disturbances in cholinergic pathways involved in fertility functions. These mechanisms cannot be either proven or completely dismissed since assessment of neurobehaviour and specific physiologic fertility functions that are regulated by cholinergic pathways were not reported for this study. In light of these uncertainties, RAC agrees on Category 2 for adverse effects on fertility for phosmet.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Belgium	Gowan Comercio Internacional e Serviços, Lda	Industry	7

Comment received

Comment on the proposed classification Acute Tox. 4, H332

Technical Phosmet displays no potential for aerosol formation and only a low potential for vapour formation. Technical Phosmet is an amorphous crystalline agglomerate with low vapour pressure which does not contain respirable or inhalable particles. Hence, the pure substance cannot be inhaled quantitatively and therefore poses no health hazard by the inhalation route of exposure as experimentally confirmed by Leong (1977). During the manufacturing of plant protection products containing Phosmet as active substance, grinding of technical Phosmet is performed in a closed automated system resulting in a complete lack of worker exposure to non-formulated ground technical Phosmet by the inhalation route.
The results of the key acute inhalation study with technical Phosmet (Leong, 1977) indicated that the 4 hour inhalation LC50 in rats was greater than 0.152 mg/L air (whole body exposure to a saturated vapour atmosphere), which was the highest concentration that could be established under the experimental conditions. In the Peer Review of Phosmet (EFSA, 2011), this view was adopted, since it is stated that 0.152 mg/L represents the maximum concentration attainable, and that experts agreed not to classify Phosmet for toxicity by inhalation.

Therefore the view is taken that technical Phosmet is not subject to classification for acute inhalation toxicity according to the CLP Regulation. A classification based on a precautionary approach, as suggested by the Spanish Competent Authority (2015), is not applicable in the case of technical Phosmet due to the lack of any significant exposure via the inhalation route under normal use conditions (no respirable particles, no acute toxicity in a saturated vapour atmosphere).

For classification, the differentiation between technical Phosmet (amorphous crystalline agglomerate without respirable particles and with low vapour pressure) on the one hand and formulated Phosmet (formulation-dependent properties in terms of aerosol formation/particle or droplet size)) on the other hand is considered adequate, and is in line with the Guidance on the application of the CLP criteria (ECHA, 2015)/Article 9(5) of the CLP Regulation, which states that the form or physical state in which the substance or mixture is placed on the market and in which it can reasonably be expected to be used shall be considered in this context. Of note, Phosmet formulations may display acute inhalation toxicity as was shown by Mould (1995) for a 70 WP formulation. Under the current provisions, such formulations must be, and are, tested and classified accordingly.

In conclusion, the proposed classification of Phosmet in Acute Tox. 4, H332 should be rejected.

References:
ECHA (2015). Guidance on the application of the CLP criteria. Version 4.1. ECHA-15-G-05-EN.
EFSA (2011). Conclusion on the peer review of the pesticide risk assessment of the active substance Phosmet. EFSA Journal 2011;9(5): 2162.
Leong KJ (1977). Acute inhalation toxicity study in albino rats – saturated atmosphere - International Research and Development Corporation, Michigan, USA. Doc. No. 523 001.
Mould A (1995). Imidan WP-70 - Acute inhalation toxicity study in rats. Hazleton Europe, Harrogate, England. Doc. No. 528-016.

Dossier Submitter's Response

The Spanish CA is aware of the problematic of generating highly respirable atmospheres of dusts and mists from materials that in practice will have lower exposure. However, according to Guidance Document on Acute Inhalation Toxicity Testing (July 21, 2009) corresponding to OECD Document no. 39 for inhalation, an explanation and supportive data should be provided to explain why the regulatory limit concentration could not be achieved. This guidance also states that if the targeted regulatory limit concentration of 5 mg/l cannot be achieved by the initial technical procedures, then at least one alternative generation method should be used, ideally using different physical principles but established methodologies.
According to data submitted by notifier it is not possible to generate respirable atmospheres of the technical material without destructive grinding of the test substance. Nevertheless, results obtained with formulated Imidan 70 WP (the only component of this formulation that potentially could induce toxicity by inhalation is phosmet) suggest that generation of toxic by inhalation respirable atmospheres with technical phosmet may be difficult but not impossible.
Since it is not clear that generation of respirable atmospheres with technical phosmet can be discarded, as a precautory approach, a classification of technical phosmet as H332, category 4, is purposed, taking into account data extrapolated from the study with formulation Imidan 70 WP.
A possible solution proposed at the meeting of ECB was to created a split entry with Xn, R20" for phosmet ≥ 70%, based on the study with the formuladed product Imidan 70 WP, "and no classification for phosmet < 70%. This split entry was, however, not accepted by MS experts during the May 2007 ECB meeting. One argument put forward for not accepting a split entry was that it seemed possible to perform a study with a proper particle size of the substance.

RAC's response

RAC supports the conclusion of the DS that according to CLP Regulation phosmet should be classified in Category 4 for acute inhalation toxicity based on the results from acute inhalation toxicity study with Phosmet formulation as wettable powder, Imidan 70 WP.

RAC disagrees with Industry's opinion that any significant exposure to phosmet via the inhalation route under normal use conditions is not expected.
In the Guidance Document on Acute Inhalation Toxicity Testing (OECD 39, July 21, 2009) it is stated that "**acute inhalation testing is not required if the physical form of a test article, as it is marketed or used, precludes any human inhalation exposure** (e.g., solid metal block, non-friable granules, composite elastic materials)", and in the Guidance on the Application of the CLP Criteria Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures (Version 4.1, June 2015) it is pointed out that regarding assessment of inhalation toxicity of substances for which inhalation exposure is not expected under realistic conditions "specific problems may arise with respect to classification and labelling, as these substances are tested in a **form** (i.e. specific particle size distribution) **that is different**

from all the forms in which these substances are placed on the market and in which they can reasonably be expected to be used".
Generation of phosmet aerosol could be expected during production of plant protection products (illustrated by Industry statement provided during Public Consultation: "During the manufacturing of plant protection products containing Phosmet as active substance, grinding of technical Phosmet is performed in a closed automated system resulting in a complete lack of worker exposure to non-formulated ground technical Phosmet by the inhalation route") and during the use of these products (e.g. for Imidan 70 WP, formulation used for acute inhalation toxicity study, MMAD±GSD of particles ranged from 1.61±2.00 μm to 2.38±1.95 μm). RAC also points out that lowering health risks by good occupational hygiene measures does not affect classification and labelling of the substance, since C&L process is hazard-based, and not risk-based.

RAC is of the opinion that in the absence of an adequate inhalation study with aerosol of technical phosmet, the results of acute inhalation study with exposure to phosmet formulation in form of wettable powder could be used for classification purposes. Other ingredients of wettable powder formulation are not expected to be relevant for toxicity of the product (please refer to revised DAR, p 339), and, indeed, clinical signs in exposed animals were typical for organophosphate poisoning (e.g. lethargy, salivation, tremors).

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Germany		MemberState	8
Comment received				
Acute oral toxicity: Based on the data presented, we support the classification in category 3 for acute oral toxicity. Acute inhalative toxicity: Based on the argumentation outlined by the MSCA in the CLH report and on the discussion presented in document: Follow up_V_0507(2).doc (pp. 8-10), we support a classification of acute inhalative toxicity category 4. Acute dermal toxicity: Based on the data presented, we support not to classify phosmet for acute dermal toxicity.				
Dossier Submitter's Response				
Thanks for your support with our proposal on acute toxicity				
RAC's response				
Thank you, RAC also agrees with acute toxicity classification proposed by the Dossier Submitter.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Belgium	Gowan Comercio Internacional e Serviços, Lda	Industry	9
Comment received				
The ECHA guidance (2015) specifies that STOT-RE is assigned on the basis of findings of 'significant' or 'severe' toxicity. In this context 'significant' means changes which clearly				

indicate functional disturbance or morphological changes which are toxicologically relevant. 'Severe' effects are generally more profound or serious than 'significant' effects and are of a considerably adverse nature which significantly impact on health. Thus, inhibition of cholinesterase should be only considered as relevant for STOT-RE classification if noted in conjunction with additional adverse effects on the nervous system, e.g. clinical signs of neurotoxicity, microscopical finding in the nervous system. For Phosmet, there was no clinical or histopathological manifestation of neurotoxicity in the key long-term repeated dose toxicity studies. As also stated in the CLH proposal (Spanish Competent Authority, 2015), Phosmet did not result in pathology or histopathology of the nervous system. In the studies identified by EFSA (2011) as key or supporting studies for the derivation of the ADI or the AOEL (Brown, 2003; Cappon, 1999; Chang et al., 1991; Johnston, 1962; Jones, 1981; Meyer and Walberg, 1990), no clinical signs of neurological action/neurotoxicity or other manifestations of neurotoxicity were noted at dose levels equal to or below the guidance value to assist in STOT RE 1 classification (≤ 10 mg/kg bw/d). Thus, the classification of Phosmet with STOT RE 1 is not appropriate.

The (A)ChE inhibition and related neurological clinical signs that were observed upon repeated dosing with Phosmet were generally fully reversible and qualitatively comparable to its acute effects across species.

In conclusion, Phosmet does not need to be classified with STOT RE Cat 1 H372: there is no Phosmet-related health hazard which (i) would have to be specifically addressed by a STOT RE (or STOT SE) classification for effects on the nervous system and which (ii) would not be covered by the existing classification for acute effects according to the CLP Regulation. This assessment is supported by the fact that STOT RE should only be assigned where the observed toxicity is not covered more appropriately by another hazard class, here acute toxicity (ECHA, 2015).

References:

Brown MA (2003). Phosmet: Dose-range-finding oral (feeding) toxicity study in the dog. RCC Ltd., Itingen, Switzerland. Doc. No. 532-008.
Cappon GD (1999). A dietary subchronic (90-day) neurotoxicity study of Phosmet in rats. WIL Research Laboratories, Ashland, Ohio. Doc. No. 542-003.
Chang JCF, Morrissey RL, Wyand S (1991). 2-year chronic toxicity-oncogenicity study with R-1504 in rats. Ciba-Geigy Corporation, Farmington, CT. Doc. No. 537-002.
ECHA (2015). Guidance on the application of the CLP criteria. Version 4.1. ECHA-15-G-05-EN.
EFSA (2011). Conclusion on the peer review of the pesticide risk assessment of the active substance Phosmet. EFSA Journal 2011;9(5): 2162.
Johnston CD (1962). An evaluation on Imidan in the rat and the dog. Woodard Research Corporation, Virginia, USA. Doc. No. 533-001.
Jones MS (1981). Four week dietary range-finding study in mice with Imidan Technical. Stauffer Chemical Company, Farmington, USA. Doc. No. 532-004.
Meyer LS, Walberg JA (1990). Two-generation reproduction study in rats with R-1504. Ciba-Geigy Corporation, Farmington, USA. Doc. No. 553-002.

Dossier Submitter's Response

The main sensitive adverse effect after oral and dermal repeated exposure of phosmet was brain and erythrocyte AChE inhibition. A statistically significant inhibition of brain, peripheral nerve or erythrocyte AChE ≥ 20% with respect to the concurrent control group or with respect to the 'pre-exposure' values in the treated group is considered toxicologically relevant ('adverse'). Even statistically significant inhibition of less than 20% or statistically insignificant inhibitions above 20% indicates that a more detailed analysis of

the data should be undertaken (JMPR, 1998; US EPA, 2000; Nielsen et al., 2008; EFSA, 2013). Inhibition of brain and erythrocyte AChE by 20% or more was obtained from subacute, subchronic and chronic studies after oral and dermal phosmet exposure as shown in section 4.7.1.8 of spanish proposal. Besides this neurochemical effect, some clinical signs typical of an organophosphorous compound were also observed in some studies after oral exposure. Furthermore, in a randomised double blind study for effects in plasma and RBC AChE in humans (Cameron, 1999) inhibition of RBC AChE was observed after single oral dose at dose levels from 1 mg/kg bw.

The EFSA Panel on Plant Protection Products and their Residues (PPR) provided a scientific Opinion (EFSA, 2013) on the identificaction of pesticides to be included in the cumulative assessment groups (CAGs) based on their toxicological profile from the basis of datasets of oral toxicity studies evaluated in the Draft Assessment Reports (DARs) for pesticides having effects on thyroid or nervous system. It was decided that data collection needed to be re-evaluated with the aim of identifying adverse effects of pesticide active substances, among others, on the nervous system. The PPR panel regarded re-evaluated data provided from an external scientific report by the Danish Technical University (DTU) published by the EFSA in 2012 and a further revision of the DTU data published in 2013 (ANSES/ICPS/RIVM). The PPR panel recognized inhibition of brain and erythrocyte cholinesterase as a neurochemical effect which represents a level of grouping for neurotoxic substances based on mechanism of action rather that on phenomenological effects. Accordingly, phosmet was grouped in the acute and chronic CAGs for the nervous system based on neurochemical endpoints (inhibition of brain AChE). It has to be noted that a chronic LOAEL of 1 mg/kg bw/day for phosmet is established in this document (EFSA, 2013) based on brain AChE inhibition.

In most studies cholinesterase inhibition remaining at the end of the studies, as shown in table 29 of Spanish Report (not being fully reversible as Industry suggested). In addition, according to CLP regulation (chapter 3.9.1.1), classification after repeated dose exposure covers all significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed are included.

In MSCA opinion, critical effects of significant inhibition of brain and erythrocite cholinesterase and clinical signs associated with neurotoxicity are considered adverse and toxicollogicaly relevant effects. The central question is whether these adverse effects observed after repeated dose exposure in several species are covered by acute toxicity. Data suggest that the doses which elicited these functional adverse effects in oral and dermal acute and repeated toxicity testings are considered to be sufficiently different to justify an additional classification for repeated dose toxicity. Similar adverse effects after repeated exposure are observed at lower doses than for single exposure.

In addition, in the above mentined EFSA publication (EFSA, 2013) it is suggested the association between environmental exposures to organophosphate pesticides such as phosmet and neurodevelopmental and neurobehavioural effects in humans. There is a growing information, in the public literature, on the effects of these compounds on the developing brain of laboratory animals indicating that gestational and/or postnatal exposure may cause persistent behavioral effects into adulthood.

Therefore, classification for STOT RE 1 is required for phosmet.

RAC's response

RAC considers that presented animal studies with phosmet did not show evidence strong enough to trigger STOT RE classification. RAC acknowledges that cut-off value of 20% cholinesterase inhibition does not separate adverse from non-adverse effects, but, according to OPP's (the Office of Pesticide Programs, US EPA) experience, rather

represents statistically significant difference compared to pre-treatment values, and thus, is generally viewed as biologically significant (US EPA 2000). In non-acute phosmet studies clinical signs typical for organophosphate poisoning were rarely described, despite inhibition of RBC and brain AChE up to 100%. RAC is aware that an assessment of adverse effects following repeated exposure to cholinesterase inhibitors could be complicated by the development of tolerance to organophosphate toxicity. This homeostatic decrease in the density of cholinergic receptors protects against acute organophosphate toxicity, but alters a balance of neuronal connections, compromising higher brain functions. Although RAC acknowledges that potential neuropsychological adverse effects of chronic, low level exposure to organophosphates in humans (without overt signs of acute poisoning) cannot be excluded (e.g. Pilkington *et al.* 2001), these studies are not specific for phosmet but refer to organophosphates as a group, and suffer from well-known limitations, inherent to population studies. In light of these uncertainties STOT RE classification is not proposed by RAC.

However, STOT SE Cat. 1, H370 (nervous system) is proposed. Namely, in acute neurotoxicity study in rats (Cappon, 1998a), clinical symptoms typical for organophosphate exposure (whole body tremors, gait alterations and salivation) were observed after single oral exposure at 36 mg/kg bw, a dose level below the Guidance value of 300 mg/kg bw for STOT SE Category 1, and below 50< ATE ≤300 mg/kg bw range that corresponds to Category 3 for acute oral toxicity proposed for phosmet. Human poisoning cases support this conclusion (e.g. Gallagher, 1990, CDC Report, 1999).

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Germany		MemberState	10
Comment received				
Based on the data presented, we support to classify phosmet for specific target organ toxicity category 1.				
Dossier Submitter's Response				
Thanks for your support.				
RAC's response				
Please see RAC response to Comment No 9.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
09.11.2015	United Kingdom		MemberState	11
Comment received				
We note, it was agreed to remove the DSD R53 classification in 2006. However, since this time guidance on data requirements to support determination as 'rapidly degradable' designation have been developed in CLP guidance. The current ECHA guidance (section 4.1.3.2.3.2) states: " A substance is considered to be not rapidly degradable unless at least one of the following is fulfilled: a. The substance is demonstrated to be readily biodegradable in a 28-day test for ready biodegradability. The pass level of the test (70 % DOC removal or 60 % theoretical oxygen demand) must be achieved within 10 days from the onset of biodegradation, if it is possible to evaluate this according to the available test data (the ten-day window condition may be waived for complex multi-component substances and the pass level applied at 28 days, as discussed in point II.2.3 of Annex II to this document). If this is				

not possible, then the pass level should be evaluated within a 14 days time window if possible, or after the end of the test; or
b. The substance is demonstrated to be ultimately degraded in a surface water simulation test with a half-life of < 16 days (corresponding to a degradation of >70 % within 28 days); or
c. The substance is demonstrated to be primarily degraded biotically or abiotically e.g. via hydroysis, in the aquatic environment with a half-life <16 days (corresponding to a degradation of >70 % within 28 days), and it can be demonstrated that the degradation products do not fulfill the criteria for classification as hazardous to the aquatic environment. "
Phosmet did not meet the readily biodegradable criteria in a ready biodegradation study.

It is currently unclear if DT50 values quoted in the CLP report relate to primary or ultimate degradation. We anticipate they reflect dissipation and hence primary degradation. On this basis, we do not consider it has been demonstrated that the phosmet is ultimately degraded with a half-life <16 days.

The CLH Report mentions ecotoxicology studies for degradants in sections 5.1.3 and 5.5. However the studies are not included in the report and their validity is not assessed. In addition it is unclear if these studies cover the three trophic levels considered for CLP. Therefore we do not feel it has been demonstrated that degradation products are non-classifiable.

On this basis we feel further information is required to support designation as rapidly degradable. This should include clarification of primary and ultimate DT50 values and evaluation of degradant ecotoxicity studies.

Reference: ECHA (2015) Guidance on the Application of the CLP Criteria. Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures. Version 4.1. June 2015

Dossier Submitter's Response

Taking into account the available information on Phosmet (Phosmet revised DAR, volume 3. 2007) from water/sediement studies, it is considered that the DT50 values are related to primary degradation of the active substance, and the degradation products are not calssified as hazardous to the aquatic environment.

Revised assessment after evaluation of statements submitted by Notifier and rapporteur member state agrees:

• The state of the art in water/sediment study indicates that the relevant metabolites identified in the polar fraction are just the same those identified from hydrolysis studies under different pH conditions, and the degradation rate is very high (Kidd, et al 2005). This states that, in natural ponds, no new pathway in degradation of phosmet is expected due to pH.
In addition, the Notifier has demonstrated that no new metabolites reach as consequence of biotic conditions.

Furthermore, because toxicological studies conducted with the relevant metabolites indicated no toxicity, toxic effects are only due to active ingredient phosmet.

The information available to relevant metabolites is:

- **Environmental metabolite O,O-Dimethylphosphoric acid**

Volz E. 2005. The purpose of this study was to determinate the acute toxicity of O,O-Dimethylphosphoric acid to the water flea Daphnia magna under static conditions along 48 hours. The test followed the OECD 202, part I guideline and it was conducted under GLP. The study is valid.

After 24 and 48 hours of exposure no immobility of the test organisms was observed in the control and up to and including the highest test item concentration of 100 mg/L.
The 48-hour NOEC of O,O-Dimethylphosphoric acid to Daphnia magna was 100 mg/L the highest rate tested The 48-hour EC50 was higher than 100 mg/L.

- **Environmental metabolite O,O-Dimethylphosphorodithioic acid potassium salt**

Volz E. 2005. The purpose of this limit study was to determinate the acute toxicity effect at 100mg/L concentration of O,O-Dimethylphosphorodithioic acid potassium salt to the water flea Daphnia magna under static conditions along 48 hours. The test followed the OECD 202, part I guideline and it was conducted under GLP. The study is valid.

In the control and in the test concentration up to and including 100 mg/L, no immobilized test organisms were observed during the test period of 48 hours.

The 48 hours LC50 on Daphnia magna is higher than 100 mg/L of O,O-Dimethylphosphorodithioic acid potassium salt. The NOEC was therefore determined to be 100 mg/L.

- **Environmental metabolite Phthalamic acid (PaA)**

Volz E. 2005 . The purpose of this study was to determinate the acute toxicity of Phthalamic acid to the water flea Daphnia magna under static conditions along 48 hours. The test followed the OECD 202, part I guideline and it was conducted under GLP. The study is valid.

In the control and in the test concentration up to and including 100 mg/L, no immobilized test organisms were observed during the test period of 48 hours.

The 48 hours LC50 on Daphnia magna is higher than 100 mg/L of Phthalamic acid. The NOEC was therefore determined to be 100 mg/L.

- **Environmental metabolite Phthalic acid**

Jonsson and Baun (2003). Environ. Toxicol. Chem, vol 22, nº 12, pp. 3037-3043, 2003. Title: Toxicity of Mono- and Diesters of o-Phthalic esters to a Crustacean, a Green Alga, and a Bacterium. The objective of this bibliographic study was to determinate the effects of Phthalic acid (> 99% purity) on immobilisation of daphnia by exposing 20 animals (less than 24 hours old) in four replicates per test level to five concentrations for 48 hours

The EC50 for daphnia was determined to be 103 mg/L after 48 hours. The 48 h-EC10 value was 6.04 mg/L.

Taking into account this information, Phosmet can be considerd as a rapidly degradable substance in the environment.
Classificaton of Aquatic Acute 1 with M-factor of 100 and Aquatic Chronic 1 with M-factor of 10 is proposed.

RAC's response
RAC agrees with UK MS in qualifying the CLH Report data and their interpretation as not being fully in line with the requirements of the CLP Guidance. Primary or ultimate degradation – this question can be decided based on the Report content, but still the comparison with the CLP criteria is missing from the Report. The second issue, the ecotoxicity of the metabolites, is completely missing from the Report; only a statement is included that the metabolites are not toxic. This statement should be supported by data: it has happened in the RCOM, where the DS included some available toxicity data of four typical metabolites. Further details are necessary on the metabolites, such as their proportion in the residue and their stability. Otherwise, RAC cannot decide if the toxicity results of the above listed four metabolites do completely fill the information gap or not. If the toxicity of other missing metabolites – mentioned in the Report by names – is negligible, due to very small proportion or very short lifetimes as intermediate metabolites, it should have been stated. DS should have clarified whether the here-mentioned four metabolic substances cover all dominant metabolites or whether the reason for not providing complete information is non-availability of toxicity data for the others.

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Germany		MemberState	12
Comment received				
We support the proposed environmental classification and labelling as Aquatic acute 1 (H400) and Aquatic chronic 1 (H410) and the acute/chronic M-factor of 100/10.				
Dossier Submitter's Response				
Thanks for your support.				
RAC's response				
Thank you for your contribution.				