Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Ethephon

EC number: 240-718-3

CAS number: 16672-87-0

ECHA/RAC/CLH-O-0000001734-74-03/A2

Adopted

19 November 2011

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

ECHA has compiled the comments received via internet that refer to several hazard classes and entered them under each of the relevant categories/headings as comprehensive as possible. Please note that some of the comments might occur under several headings when splitting the given information is not reasonable.

Substance name: Ethephon
EC number: 240-718-3
CAS number: 16672-87-0

General comments

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
29/06/2011	Spain / MSCA	We are in agreement with the environmental classification proposal made by NL.	Thank you for the support	No Comment (NC)
11/07/2011	Spain / MSCA	In general terms, the Spanish CA supports the Dutch proposal for ethephon harmonised classification & labelling. However, we propose an additional classification as Xi; R37: Irritating to respiratory system, according to Directive 67/548/EC, and a change in the subcategory of corrosion from 1B to 1C for a final classification as Skin Corr. 1C H314: Causes severe skin burns and eye damage, according to Regulation EC 1272/2008.	See below	Agree Skin Corr. 1C H314: Causes severe skin burns and eye damage. The RAC does not agree with the application of Xi; R37: Irritating to respiratory system and supports the position of the MSCA who proposes to remove STOT SE 3 and to classify with EUH071 (Corrosive to the respiratory tract)

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
				for the reasons outlined below.
14/07/2011	Belgium /MSCA	We agree with the proposed classification.	Thank you for the support	NC
18/07/2011	Portugal / National Authority	Considering the present proposal, we agree with the need to establish a revised harmonised classification & labelling for Ethephon. We support the removal of the Classification and Labelling for the environment as the substance doesn't fulfil the criteria established both in CLP Regulation and 67/548/EEC Directive. Nevertheless, we have detected some editorial inaccuracies on pages 4, 5, 7 and 8: -Page 4: The reference to "Ethephon was included in Annex I of Directive 67/548 in 2004 … TC C&L agreed ethephon does no need to be classified for sensitization and as Xn; R20/21/22 – C; R34. …", should be changed to "Ethephon was included in Annex I of Directive 67/548 in 2004 … TC C&L agreed ethephon need to be classified for sensitization and as Xn; R20/21/22 – C; R34. …"; -Page 5: for consistency reasons "STOT-SE Cat.3; H335" should be changed to "STOT SE 3; H335"; -Page 7: the concentration limit "5%<C<10% Xi; R36/37/38" should be changed to "5%≤C<10% Xi; R36/37/38"; -Page 8: for consistency reasons "C ≥ 5 % H335" should be changed to "C ≥ 5 % STOT SE 3; H335". We also support the introduction of the STOT classification as "STOT SE 3; H335.	Thank you for the support. We have adapted the editorial inaccuracies. The classification and specific concentration limit for STOT SE 3 has been removed, for reasons explained below	NC
22/07/2011	Germany / Bayer CropScience	Classification for acute dermal toxicity should not be applied, because ethephon is a corrosive compound and is already classified as such. In addition, an acute dermal toxicity study should not be performed with a corrosive compounds, in agreement with the current regulatory requirements.	We agree that a dermal toxicity study should not have been performed, due to the low pH of the substance. However,	RAC acknowledges that a dermal toxicity study should not have been conducted

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
			a study is available and can be used for classification purposes. Although skin necrosis was observed during this study, we do not agree that the clinical effects observed in the rabbits are only the result of corrosion. Since it cannot be excluded that at least part of the effects are unrelated to the corrosive properties, the substance should be classifiied for acute dermal toxicity as proposed, based on the LD50 in females.	but as it is available, should be considered in the classification proposal. As described by the MSCA, acute toxicity and corrosion are different endpoints although for ethephon are likely to be interrelated. We agree to the classification proposal on the basis of the acute dermal data.
27/07/2011	Germany / MSCA	The German CA supports the proposed harmonized classification. Report Page 9 & IUCLID Chapter 1.2: In IUCLID chapter 1.2, two impurities are listed. In the report none of these impurities are stated in chapter 1.2 Composition of the substance. Moreover, it is said in the documents that „Further information on impurities is confidential" but no confidential document is attached. As a consequence, no detailed composition of Ethephon is stated in the documents for C&L. DE is of the opinion that the detailed composition of a substance should be given. Confidential information can be included in the IUCLID file and be flagged as such or, alternatively, a confidential annex can be attached to the Annex VI report. In the report on page 6 there is a typo (heading "Proposed labelling on	Thank you for the support. We have included some information on the impurities MEPHA and 1,2-Dichloroethane in 1.2 of the report. However, we do not have access to the confidential information, which is therefore not	NC

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		Directive 67/548/EEC"): The symbol N should be deleted. The symbol "Xn" is optional for compounds labelled with "C".	included (as confidential) in IUCLID or the Annex VI report. We have removed the symbol N and Xn.	
28/07/2011	Sweden / MSCA	In absence of any new data Sweden supports the agreement, on the proposed classification and labelling for Ethepon (CAS number 16672-87-0, EC number 240-718-3), taken by the Technical Committee on Classification and Labelling (Directive 67/548/EEC) ('TC C&L').	Thank you for the support	NC
28/07/2011	United Kingdom / UK Competent Authority / MSCA	We generally agree with the classification proposed for Ethephon in accordance with both Dir 67/548/EEC and CLP. However, we have a number of comments regarding the dossier as detailed in the specific sections below which require clarification. On page 6 the labelling in accordance with Dir 67/548/EEC is provided. This includes the symbol N, even though the proposal is to remove the environmental classification. Please remove this.	Thank you for the support We have removed the symbol N	NC
29/07/2011	France / MSCA	France is agree with the classification proposal and has no comments.	Thank you for the support	NC
30/09/2011			With reviewing the annex VI dossier, we have made the following editorial changes to improve the quality of the dossier: Page 4: ethephon base is a 71% dilution on average. We have added a range.	RAC agrees with the amendments

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
			Page 4: ethephon does not need to be classified for sensitisation according to the TCC&L (typo). 5.2 Acute toxicity: We have corrected the LD50 values as there were some calculation errors in the correction for the purity of the active substance.	

Carcinogenicity

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
27/07/2011	Germany / MSCA	The German CA supports not to classify Ethephon for carcinogenicity.	Thank you for the support	RAC agrees
28/07/2011	United Kingdom / UK Competent Authority / MSCA	We agree that the data in the proposal do not support classification for carcinogenicity. However, is it possible to provide historical control data where appropriate? For example, it mentions on page 40 that lung adenomas commonly occur in this strain of mouse.	We agree that historical control data would be helpful. However, they are not mentioned in the DAR.	The mouse strain is not mentioned (in the DAR either). The historical data could be obtained if this information was available.

Mutagenicity

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
27/07/2011	Germany / MSCA	The German CA supports not to classify Ethephon for mutagenicity.	Thank you for the support	RAC agrees
28/07/2011	United Kingdom / UK Competent Authority / MSCA	We agree that the data in the proposal do not support classification for mutagenicity.	Thank you for the support	RAC agrees

Toxicity to reproduction

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
27/07/2011	Germany / MSCA	The German CA supports not to classify Ethephon for reproductive or developmental toxicity.	Thank you for the support	RAC agrees
28/07/2011	United Kingdom / UK Competent Authority / MSCA	We agree that the data in the proposal do not support classification for reproductive toxicity.	Thank you for the support	RAC agrees

Respiratory sensitisation

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
28/07/2011	United Kingdom/ UK Competent Authority/ MSCA	There are no data in the proposal to support classification for this hazard class.	Thank you for the support	RAC agrees

Other hazards and endpoints

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
11/07/20	Spain / MSCA	p. 5 Proposed classification based on Regulation EC 1272/2008	The labelling has been	Noted

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
11		Taking into account Regulation EC 286/2011, which modifies the Regulation EC 1272/2008, the hazard statement codes H302 and H332 must be combined as H302+H332.	adapted.	
		p. 26 Summary and discussion of acute toxicity Acute oral toxicity The Spanish CA supports the proposed classification of ethephon as Acute Tox. 4 (oral) (H302: Harmful if swallowed) (300<LD50≤2000 mg/kg bw) according to Regulation EC 1272/2008 and as Xn; R22: Harmful if swallowed (300<LD50≤2000 mg/kg bw) according to Directive 67/548/EC. This classification is due to the LD50 value obtained in females in an acute oral toxicity study in rats (Meyers, 1989a): LD50 females= 1563 mg/kg bw (corrected results for the pure active substance).	Thank you for the support with regard to the classification for acute toxicity and respiratory irritation.	Noted
		Acute dermal toxicity The Spanish CA supports the proposed classification of ethephon as Acute Tox. 3 (dermal) H311: Toxic in contact with skin (200<LD50≤1000 mg/kg bw) according to Regulation EC 1272/2008 and as Xn; R21: Harmful in contact with skin (400<LD50≤2000 mg/kg bw) according to Directive 67/548/EC. This classification is due to the LD50 values obtained in females in an acute dermal toxicity study in rats (Meyers, 1989b): LD50 females= 983 mg/kg bw (corrected results for the pure active substance).	We agree that, since in the skin irritation study necrosis was only observed after a 4 hour exposure period and not after a 1 hour period, classification as Skin Corr1C indeed is more appropriate. We do not agree with classification as R37. This is implicit, since the substance is already classified as R34, with a SCL for R36/37/38	Agreed RAC agrees with the DS
		Acute inhalation toxicity The Spanish CA supports the proposed classification of ethephon as Acute Tox. 4 (inhalation) H332: Toxic in contact with skin (1<LC50≤5 mg/kg bw) according to Regulation EC 1272/2008 and as Xn; R20 Harmful by inhalation (1<LC50≤5 mg/kg bw) according to Directive 67/548/EC. This classification is due to the LC50 values obtained in an acute inhalation toxicity study in rats (Nachreiner and Klonne, 1989): LC50 = 3.20 mg/L (corrected results for the pure active substance).	The classification and specific concentration limit for STOT SE 3 has been removed, for reasons explained below	
		p. 27 Summary and discussion of irritation		

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		The Spanish CA supports a classification as C; R34: Causes burns based on the results of the 4-hour exposition performed corrosion study (Meyers, 1983) according to Directive 67/548/EC. However, according to Regulation EC 1272/2008, we propose a change in the subcategory of corrosion from 1B to 1C resulting in a classification as Skin Corr. 1C H314: Causes severe skin burns and eye damage, taking into account the fact that the signs of necrosis in the skin corrosion study (Meyers, 1983) were observed only after 4-hour exposition. The Spanish CA supports the proposed classification of ethephon as STOT SE 3 H335: May cause respiratory irritation according to Regulation EC 1272/2008. Additionally we propose a classification as R37: Irritating to respiratory system, according to Directive 67/548/EC, considering the signs of respiratory tract irritation observed in the acute inhalation study (Nachreiner and Klonne, 1989).		
14/07/2011	Belgium / MSCA	Some editorial or/and minor comments on environmental endpoints : • p.6. Please delete "N" as symbol in the proposed labelling on dir.67/548/EEC • please make a clear distinction, for the aquatic toxicity endpoints, in the values between the technical concentrate and ethephon pure substance. •p.18. 4.1.2.2 simulation tests : degradation in water/sediment systems : Please mention the guideline according to which the test was carried out.	 The symbol "N" was removed. Adjusted Adjusted	Noted
22/07/2011	Comment submitter's identity is confidential	Classification for acute dermal toxicity should not be applied, as further explained in the attached position paper *ECHA comment: The document attached is copied below without document's title according to confidential:* **Impact of corrosivity properties on classification after dermal exposure** Ethephon is produced and marketed in a water dilution so called Ethephon Base 250 (CropLife-code TK). The specification of this technical concentrate material (TK) in pure active substance is : minimum purity 69.2 % w/w and maximum purity 73.5 % w/w. The ethephon technical material (TC) is only a transient step during the manufacturing process of	We agree that a dermal toxicity study should not have been performed, due to the low pH of the substance. However, a study is available and can be used for classification purposes. Although skin necrosis was observed during this study, we do not agree that the clinical effects observed in the rabbits are only the result of corrosion.	RAC agrees with the MSCA (DS)

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		the Ethephon Base 250 technical concentrate material (TK). Indeed, additional water is intentionally added to bring the final product to label specifications of Ethephon Base 250 (TK). This water addition is necessary for homogeneity and further transportation of the Ethephon Base 250 (TK) which is a solution in water. Ethephon Base 250 TK has a pH of 1.6 and corrosive properties to the skin. It is classified R34 or H314. Therefore, toxicity studies via the dermal route at doses that could cause marked pain and distress due to the corrosive properties should not be carried out. However, an acute dermal toxicity in rabbits was carried out in 1983 in accordance with FIFRA Test Guideline 1982 (not OECD 402) using doses of 2780, 1390 and 685 mg Ethephon Base 250 TK/kg bw (M-188169-01-1). Applications were made to shaved areas on the dorsal trunk skin surface, with an occlusive binding. Each animal was placed in a restrainer where it remained for 24 hours, after which it was removed and any residual test material carefully wiped off. In all animals these dose levels provoked dose-related severe dermal effects, i.e. skin necrosis and erythema and sores for at least one week. All the top dose animals died the day of exposure and all animals presented skin necrosis. One male and two females exposed to 1390 mg Ethephon Base 250/kg bw died within three days and presented necrosis and erythema as well. One female of the 685 mg/kg bw group died the first day during application. A summary of the results is given in the below table	Since it cannot be excluded that at least part of the effects are unrelated to the corrosive properties, the substance should be classifiied for acute dermal toxicity as proposed, based on the LD50 in females.	

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment

Table 1: Acute dermal toxicity of Ethephon Base 250: correlation within death and skin effect

	Males			Females		
Dose (mg/kg bw)	Mortality	Time of death (day)	Skin effect on death animals	Mortality	Time of death (day)	Skin effects on death animals
2780	5/5	1	Necrosis	5/5	1	Necrosis & erythema
1390	1/5	3	Necrosis	2/5	2-3	Erythema
685	0/5	-	-	1/5	1	Necrosis

During exposure and/or before their death, animals presented various clinical signs like pinpoint
pupils, salivation, unsteady gait, and prostration. At necropsy, there were various findings which
included red lungs, red trachea, mottled livers, and intestines filled with paste-like faecal matter.

Overall the results clearly indicate that the mortality was linked to the corrosive skin effects.
Moreover, the animals were undoubtedly under marked pain and distress due to the fact that they
were restrained during the 24-hour application of the corrosive test material on their skin.

The acute dermal LD_{50} of ethephon Base 250 was calculated to be 1560 mg/kg bw for both sexes combined (LD_{50} males 1710 mg/kg bw, LD_{50} females 1390 mg/kg bw). Corrected for the pure active
substance, this results in an acute oral LD_{50} of ethephon of 1117 mg/kg bw for both sexes combined
(LD_{50} males 1210 mg/kg bw, LD_{50} females 983 mg/kg bw).

As the LD_{50} in females only for the active ingredient was calculated to be below 1000 mg/kg bw, in
the draft Annex VI report for harmonised classification and labelling proposes to classify Ethephon
Base 250 TK in Acute Category 3 (H311) for Health hazards according to the Regulation EC
1272/2008 (2)

Conclusion

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		Since mortality was secondary to corrosion, distress and pain intensified by the restrainement during the 24-hour application, it is not appropriate to classify ethephon for acute toxicity after the exposure via the dermal route. *ECHA comment: The company name has been removed according to business confidential.* As ethephon is appropriately classified as corrosive to the skin, (company) considers that no additional classification for acute effects after dermal exposure should apply. **References** 1) Myers, R.C, (1989) Ethephon Base 250. Acute percutaneous toxicity study. Dart No (M-188169-01-1). 2) Annex VI report of the proposal for harmonised classification and labelling		
27/07/2011	Germany / MSCA	Acute dermal toxicity: Based on the LD50 in female New Zealand White rabbits of 983 mg/kg bw Ethephon we agree to the proposed classification with Acute Tox Category 3, H311 according to Regulation No. 1272/2008 and Xn; R21 according to 67/548/EEC respectively. Please check the acute dermal LD50 for Ethephon (both sexes combined, 1517 mg/kg bw) on page 26. The LD50 values for males and females were corrected for the purity (70.75 %); however the value for sexes combined was corrected with 97 %. Probably it should read 1103.7 mg/kg bw. Acute oral toxicity: Based in the LD50 in female Hilltop-Wistar rats of 1563 mg/kg bw Ethephon we agree to the proposed classification with Acute Tox Category 4, H302 according to Regulation No. 1272/2008 and Xn; R22 according to 67/548/EEC respectively. Acute inhalation toxicity: We agree to classify with R20/H332. Considering the observed findings (audible respiration, discolouration of lungs) in the inhalation study and the skin corrosive properties, a	Thank you for the support with regard to the classification for acute toxicity and STOT SE. We have adapted the LD50 value (sexes combined) in the acute dermal study. We agree that, since in the skin irritation study necrosis was only observed after a 4 hour exposure period and not after a 1 hour period, classification as Skin Corr1C indeed is more appropriate We agree that classification as STOT SE 3 (H335) and labelling as EUH071 might be double. According to the CLP guidance 3.8.2.5 'It is a reasonable assumption that corrosive substances may also cause respiratory tract irritation when inhaled at exposure concentrations below those causing	RAC agrees with DS Agree RAC agrees with DS

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		classification with EUH071 seems appropriate. Skin Corrosivity: We agree to classify for corrosivity (R34, H 314). Considering the time until necrosis was observed, it might be appropriate to assign the compound into category 1C. STOT SE: Concerning the observed effects in the acute inhalation study as described in the report, we agree with the proposal to classify Ethephon for transient target organ effects with STOT SE 3 (H335). Guidance from RAC is requested for cases respiratory tract corrosion/irritation and mortalities after inhalation are observed: shall both hazard phrases, EUH071 and H335, be applied?	frank respiratory tract corrosion. If there is evidence from animal studies or from human experience to support this then Category 3 may be appropriate. In general, a classification for corrosivity is considered to implicitly cover the potential to cause RTI and so the additional Category 3 is considered to be superfluous, although it can be assigned at the discretion of the classifier. The Category 3 classification would occur only when more severe effects in the respiratory system are not observed.´ Since we propose to classify ethephon as corrosive and additionally label the substance as corrosive to the respiratory tract, classification as STOT SE 3 would be double classification. We therefore propose to remove the classification and specific concentration limit for STOT SE 3.	
28/07/2011	United Kingdom / UK Competent Authority / MSCA	Section 5.4 - Corrosivity We agree that the substance meets the criteria for classification with R34 in accordance with Dir 67/548/EEC as agreed by TCC&L. This classification is generally translated to Skin Corr. 1B in accordance with CLP as the data are not usually available to enable a distinction to be made between Cat 1B and Cat 1C. However, in this particular case, data are available following a 1 hour application period which indicate that classification in Cat 1C may be more appropriate. It is questionable whether an additional classification of EUH071 (Corrosive to the respiratory tract) or STOT SE H335 (may cause respiratory tract irritation) is required for this substance considering the available information. However, if	We agree that, since in the skin irritation study necrosis was only observed after a 4 hour exposure period and not after a 1 hour period, classification as Skin Corr1C indeed is more appropriate. According to the CLP guidance 3.8.2.5 'It is a reasonable assumption that corrosive substances may also cause respiratory tract irritation when inhaled at exposure concentrations below those causing frank respiratory tract corrosion. If there is evidence from animal studies or from human experience to support this then Category 3 may be appropriate. In general, a classification for corrosivity is	Agree

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		it is considered that such classification is required, it is not clear how they would both be applied. That is, the generic concentration limit for application of Skin Corr 1 is >= 5%. What would be applied at a concentration >= 5% H335 – 'May cause respiratory irritation' or EUH071 – 'Corrosive to the respiratory tract'? Section 5 - Environmental Hazard Assessment The current proposal includes a Lemna sp growth inhibition study which was not previously considered for classification. While effects were observed at all exposure concentrations, the 14 day growth reduction NOEC for Lemna was ≤0.1mg/l based on measured data (nominally ≤0.9mg/l). The study was run below neutral pH with stable exposure concentrations. Ethephon did not previously exhibit toxicity to algae in the same range with NOECs >1mg/l and we note this may be due to ethephon hydrolysing in algal studies run at neutral to alkaline pH. Despite ethephon rapidly degrading to ethylene (which is not classified for the environment) the Lemna study shows ethephon exhibits ecotoxicity to aquatic plants. As the Lemna NOEC is considered valid it should be considered for chronic classification.	considered to implicitly cover the potential to cause RTI and so the additional Category 3 is considered to be superfluous, although it can be assigned at the discretion of the classifier. The Category 3 classification would occur only when more severe effects in the respiratory system are not observed.´ Since we propose to classify ethephon as corrosive and additionally label the substance as corrosive to the respiratory tract, classification as STOT SE 3 would be double classification. We therefore propose to remove the classification and specific concentration limit for STOT SE 3. The classification for aquatic hazards has been revised according to the second ATP.	

ATTACHMENTS RECEIVED:
Other hazards and endpoints
Undisclosed document from a company

REFFERENCES:
Other hazards and endpoints
Annex VI report of the proposal for harmonised classification and labelling
Meyers (1983).
Meyers (1989a).
Meyers (1989b).
Myers, R.C, (1989) Ethephon Base 250. Acute percutaneous toxicity study. Dart No (M-188169-01-1).
Nachreiner and Klonne (1989).