Committee for Risk Assessment
RAC

Annex 1

Background document

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

Ethephon

EC number: 240-718-3
CAS number: 16672-87-0

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation.

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Adopted

19 November 2012

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PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: Ethephon

EC Number: 240-718-3

CAS number: 16672-87-0

Registration number (s):

Purity: *Ethephon technical*: ≥ 910 g/kg

Ethephon technical concentrate: 692 - 735 g/kg.

Impurities: *Ethephon technical*:

MEPHA: Mono 2-chloroethyl ester, 2-chloroethyl phosphonic acid: Maximum 20 g/kg

1,2-Dichloroethane: Maximum 0.5 g/kg

Ethephon technical concentrate:

MEPHA: Mono 2-chloroethyl ester, 2-chloroethyl phosphonic acid: Maximum 2 % of the ethephon declared content

1,2-Dichloroethane: Maximum 0.04 % of the ethephon declared content

Water: the water content shall be measured (g/kg) and the value obtained shall not be less than the following figure:

(1000 - (measured ethephon content in g/kg)/0.91) - 15

Further information on isomers, impurities and additives is confidential

The material produced and commercialised, is ethephon base 250, which is a 71% dilution in average (min. purity 69.2% w/w, maximum purity 73.5% w/w) of the active substance in water. However, since the water in ethephon base 250 is not a stabilizer or an impurity but a solvent that can be separated without affecting the stability of the substance or changing its composition, classification for this substance is based on the intrinsic properties of the pure substance.

Ethephon was included in Annex I of Directive 67/548 in 2004 (29th ATP; Commission Directive 2004/73/EC of 29 April). A discussion regarding a change of the classification took place at the TC C&L in November 2006 (latest Summary record ECB/20/07, see Annex I). The TC C&L discussion was related to acute toxicity, skin sensitization and corrosivity. TC C&L agreed ethephon needs to be classified as Xn; R20/21/22 – C; R34. Based on the majority opinion of the TC C&L, ethephon does not need to be classified for sensitisation. This TC C&L conclusion was, however, not included in Annex I of Directive EC 67/548 and consequently Annex VI of Regulation EC 1272/2008 still includes the previous C&L regarding human health.

A discussion regarding change of classification of ethephon for the environment took place at the TC C&L in January 2007 (Summary record ECB/08/07, see Annex II). Based on the rapid degradation of ethephon and the formation of non-classifiable metabolites, TC C&L decided not to classify ethephon as hazardous to the environment within the framework of Directive 67/548/EEC.

No registration dossiers were available for ethephon on 24 May 2011.

OPINION OF RAC

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

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard state-ment Code(s)	Pictogram, Signal Word Code(s)	Hazard state ment Code(s)	Suppl. Hazard statement Code(s)		
015-154-00-4	Ethephon; 2-chloroethylphosphonic acid	240-718-3	16672-87-0	Acute Tox 3 Acute Tox 4 Acute Tox 4 Skin Corr. 1C Aquatic Chronic 2	H311 H332 H302 H314 H411	GHS05 GHS06 GHS09 Dgr	H311 H332 H302 H314 H411	EUH071		

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
015-154-00-4	Ethephon; 2-chloroethylphosphonic acid	240-718-3	16672-87-0	Xn; R20/21/22 C; R34 N; R51-53	C R: 20/21/22-34-51/53 S: (1/2)-26-36/37/38-45-61	Xi; R37: 5 %< C < 10 %	

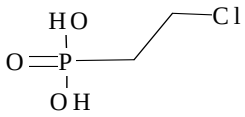
JUSTIFICATION

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Chemical Name:	(2-chloroethyl)phosphonic acid
EC Name:	2-chloroethylphosphonic acid
CAS Name:	Phosphonic acid, P-(2-chloroethyl)-
CAS Number:	16672-87-0
EC Number:	240-718-3
IUPAC Name:	(2-chloroethyl)phosphonic acid
Other Name:	Ethephon
CIPAC Number:	373
Manufacturer's development code number:	AE F016382
Annex VI index number:	015-154-00-4

1.2 Composition of the substance

Chemical Name:	(2-chloroethyl)phosphonic acid
EC Number:	240-718-3
CAS Number:	16672-87-0
IUPAC Name:	(2-chloroethyl)phosphonic acid
Molecular Formula:	$C_2H_6ClO_3P$
Structural Formula:	
Molecular Weight:	144.5
Typical concentration (% w/w):	
Concentration range (% w/w):	The minimum purity of ethephon technical concentrate is 69.2 w/w% and the maximum 73.5 w/w%. The minimum purity of the dry technical material is 910 g/kg (technical dry material - TC).

Ethephon technical contains MEPHA (Mono 2-chloroethyl ester, 2-chloroethyl phosphonic acid) in a concentration of ≤ 2% and 1,2-Dichloroethane in a concentration of ≤ 0.05%. Ethephon technical concentrate contains MEPHA in a concentration of ≤ 2 % of the ethephon declared

content and 1,2-Dichloroethane in a concentration of ≤ 0.04 % of the ethephon declared content. Further information on isomers, impurities and additives is confidential.

The material produced and commercialised, is ethephon base 250, which is a 71% dilution of the active substance in water. However, since the water in base 250 is not a stabilizer or an impurity but a solvent that can be separated without affecting the stability of the substance or changing its composition, classification for this substance is based on the intrinsic properties of the pure substance.

1.3 Physico-chemical properties

Table 1: Summary of physico- chemical properties

REACH ref Annex, §	Property	IUCLID section	Value
VII, 7.1	Physical state at 20°C and 101.3 KPa	3.1	White crystalline powder with no characteristic odour
VII, 7.2	Melting/freezing point	3.2	73.3 °C
VII, 7.3	Boiling point	3.3	Thermal decomposition
VII, 7.4	Relative density	3.4 density	1.65 kg/m^3 at 20 °C
VII, 7.5	Vapour pressure	3.6	20 °C: <10^{-3} Pa Estimation; vapour pressure was below the lower detection limit (<10^{-3} Pa) in the whole temperature range from 18 to 80 °C
VII, 7.6	Surface tension	3.10	68.5 mN/m @ 20 °C.
VII, 7.7	Water solubility (method not specified)	3.8	@ pH <0.2: >1000 g/L @ pH 4: 800 g/L. At pH 5 and above turbidity arises from gas production that became stronger with increasing pH value. Gas production indicated decomposition.
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7 partition coefficient	Log P_{ow} = -0.63 @ pH 2, room temp. Log P_{ow} = -1.89 @ pH 7, room temp. Log P_{ow} = -1.81 @ pH 10, room temp.
VII, 7.9	Flash point	3.11	No flash point up to 111 °C
VII, 7.10	Flammability	3.13	self ignition temperature: 490 °C
VII, 7.11	Explosive properties	3.14	Not explosive.
VII, 7.12	Self-ignition temperature		490 °C
VII, 7.13	Oxidising properties	3.15	The molecule only contains a chloroethylphosphonic acid and does not contain substituents or radical which has oxidative properties, also technical ethephon is a solution of 71% ethephon in water.
VII, 7.14	Granulometry	3.5	-
XI, 7.15	Stability in organic solvents and identity of relevant degradation products	3.17	-
XI, 7.16	Dissociation constant	3.21	pK_1 = 2.82 @ 21 °C pK_2 = 7.21 @ 21 °C
XI, 7.17	Viscosity	3.22	-
	Auto flammability	3.12	-
	Reactivity towards container material	3.18	-

	Thermal stability	3.19	Exothermic decomposition in the temperature range 250 - 400 °C (under nitrogen)
	Henry's law constant		$<1.45 \times 10^{-7}$ Pa $m^3 mol^{-1}$
	Solubility in organic solvents		Solvent: Solubility at 20 °C n-heptane: <0.3 mg/L p-xylene: 82.5 mg/L 1,2-dichloro-ethane: 832 mg/L acetone: >600 g/L methanol: >600 g/L ethyl acetate: >600 g/L acetonitrile: >600 g/L dimethylsulfoxide: >600 g/L
	Hydrolysis rate		Half-lives @ 25 °C: 73.5 days @ pH 5, 2.4 days @ pH 7, 1.0 day @ pH 9 Only degradate ethylene, max. 22.8%, 81.0% and 70.8% at pH 5, 7 and 9 respectively.

The above data are obtained from the Draft Assessment Report and Proposed Decision of the Netherlands prepared in the context of the possible inclusion of the active substance ethephon in Annex I of Council Directive 91/414/EEC (revised DAR January 2006, RMS The Netherlands).

2 MANUFACTURE AND USES

Not relevant for this type of report.

3 CLASSIFICATION AND LABELLING

3.1 Classification in Annex VI of Regulation EC 1272/2008

According to table 3.1 of Annex VI (index no 015-154-00-4), ethephon is classified as

Hazard class: Acute Tox 4 (minimum classification)
Acute Tox 4 (minimum classification)
Skin Corr. 1B
Aquatic Chronic 3

Hazard Statement: H332
H312
H314
H412

Spec. concentration limit: STOT SE 3; H335: C ≥ 5 %

M factor: -

According to table 3.2 of Annex VI, ethephon is classified as

Classification: Xn; R20/21
C; R34
R52-53

Risk phrases: R20/21: Harmful by inhalation and in contact with skin
R34: Causes burns
R52-53: Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment

Safety phrases: S1/2: Keep locked up and out of the reach of children
S23: Do not breathe gas/fumes/vapour/spray (appropriate wording to be specified by the manufacturer)
S26: In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
S28: After contact with skin, wash immediately with plenty of … (to be specified by the manufacturer)
S36/37/39: Wear suitable protective clothing, gloves and eye/face protection
S45: In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)
S61: Avoid release to the environment. Refer to special instructions/Safety data sheets

Specific Concentration limits: C; R34: C ≥ 10 %

Xi; R36/37/38: 5 % ≤ C < 10 %

3.2 Self classification(s)

Justified proposals for classification and labelling of **ethephon**, relating to human health and ecotoxicological effects, according to Directive 67/548/EEC are listed below:

Health hazards:

Hazard symbol:	C
Indications of danger:	Corrosive
Risk phrases:	R21; Harmful in contact with skin
	R20; Harmful by inhalation
	R34; Causes burns
	(R43; May cause sensitisation by skin contact)
Safety phrases:	S26; In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
	S36/37/39; Wear suitable protective clothing, gloves and eye/face protection
	S45; In case of accident or if you feel unwell seek medical advice immediately (show the label where possible)

Justification for the proposal:

R21: Based on the results of the acute dermal toxicity study (LD_{50} 983 mg/kg bw).

R20: Based on the results of the acute inhalation study (LC_{50} 3.26 mg/L)

R34: Based on the results of the skin irritation study (necrosis after 4 hours exposure)

(R43: Evidence of skin sensitization – inconclusive due to corrosive properties (LLNA and Maximisation test))

The substance was not labelled with R41, since R34 was already assigned

S26: Required for substances labelled with R34.

S36: Required for substances labelled with R21, S24 (required for substances labelled with R43) is not required if the substance is already ascribed with S36.

S37: Required for substances labelled with R21 and R43.

S39: Required for substances labelled with R34.

S45: Required for substances labelled with R34.

Environment

In the acute toxicity tests with ethephon the 48h-EC50 for mobility of Daphnia magna was 721 mg a.s/L. In an acute test with the rainbow trout the 96h-EC50 was 519 mg ethephon/L; there were no acute effects observed in a 96h test with carp at 100 mg ethephon/L. Three limit tests with algae indicated 120h-EC50 values > 1 mg/L. There was only one algae test with ethephon in which a range of test substance concentrations was tested. From the results of this test, RMS calculated a nominal 72h-ErC50 of 33 mg ethephon/L.
The hydrolysis DT50 value of ethephon in water was 2.5d. In a water/sediment test with two water/sediment systems DT50 values of 2.7d and 3d were determined. This indicates a very rapid degradation of ethephon in the aquatic environment.

Based on these data and on the log Pow (< 3), the applicant proposes that according to 67/548/EEC "Dangerous substance Directive", an environmental classification is not required.

4 ENVIRONMENTAL FATE PROPERTIES

The current proposal is a revision of the current entry in Annex VI to the CLP regulation (29th ATP, 2004). The environmental fate properties assessment for ethephon is based on the Draft Assessment Report, the Addendum to the Draft Assessment Report and Proposed Decision of the Netherlands prepared in the context of the possible inclusion of ethephon in Annex I of Council Directive 91/414/EEC (DAR January 2006 + addendum June 2008, RMS The Netherlands) concerning placing ethephon in the market as a plant protection product (PPP).

Ethephon was also discussed in the TC-C&L in January 2007 (Summary record ECB/08/07) within the framework of Directive 67/548/EEC. The conclusion of this discussion was that ethephon needed not be classified for the environment. A summary of the discussion can be found in Annex 2.

The current classification proposal takes into account the criteria for classification for the aquatic environment which are included in the 2nd ATP to the CLP Regulation.

All tables in the present assessment are copied from the DAR or the addendum to the DAR. The tables are renumbered in accordance with the paragraph numbers.

4.1 Degradation

4.1.1 Stability

Hydrolysis

The hydrolysis of [ethyl(U)-14C]ethephon in aqueous media was studied according to the US EPA Pesticide Assessment Guideline, Subdivision N, Section 161-1. In the hydrolysis study, carried out at three pH levels (5, 7 and 9), ethylene gas was detected as degradation product, together with phosphoric acid. The test was carried out in the dark in a biological incubator at 25 ± 1°C.
Recalculated half life times, also reverted to a temperature of 20°C are given in Table 4.1.1-1.

Table 4.1.1-1. Half-lives of ethephon in hydrolysis test

pH value	Calculated by the authors (25°C)	Calculated by RMS	Calculated by RMS and converted to 20°C
pH = 5	73.5 days	66.4 days (extrapolated value, as 50% hydrolysis was not reached)	99.1 days (extrapolated value, as 50% hydrolysis was not reached)
pH = 7	2.4 days	1.7 days	2.5 days
pH = 9	1.0 days	0.93 days	1.4 days

It was thus shown in a laboratory study that ethephon hydrolyses at pH 5, 7 and 9. Under neutral and alkaline conditions ethephon hydrolyses much faster than under acidic conditions.

Photolysis in water

The aqueous photolysis of ethephon was studied according to US EPA (Subdivision N, 161-2, 1982) guidelines. The study was carried out in an acetate buffer at pH = 5. The total test duration was 360 hours. Test vessels was exposed to artificial sunlight (> 290 nm) using a Xenon arc lamp with a mean measured intensity of 510.5 Watts/m^2 (continuous radiation) at 25 ± 1°C. A dark control was included

Ethylene gas and phosphoric acid were detected as degradation products under both irradiated and dark conditions. In the later case, the degradation is probably due to hydrolysis as the same degradations products are formed. The calculated DT50 values under irradiated and dark condition, using first order kinetic equations, were 29.4 and 51.4 days, respectively. These are extrapolated values, as 50% degradation was not achieved within the time period of the experiment.

Photolysis in soil

The degradation of ethephon in a clay loamy soil was determined after surface application. The degradation was followed for 30 days. The clay loam soil had not received any pesticide treatment for more than ten years and was collected from an agricultural site at Ongar (UK). The study was carried out at 20 ± 2°C. The major radio-labelled compound identified was ^{14}C-ethephon (99.11% at day 0, 32.55% at day 30). In the soil extract of the irradiated soil samples small amounts of 2-hydroxyethanephosphonic acid (2-HEPA) were detected (max. 10.6% applied radioactivity (a.r.) after 10 days, decreasing to 8.7% a.r. after 30 days). In addition, four minor metabolites are formed at levels below 3% a.r. These compounds were not characterized.

In the non-irradiated soil samples small amounts of 2-hydroxyethanephosphonic acid (2-HEPA) were detected in the soil extract (max. 5.7% a.r. after 30 days), together with four minor metabolites at levels below 3% a.r. The minor metabolites were not characterized. Table 4.1.1-2 presents the calculated DT50 en DT90 values.

Table 4.1.1-2. DT50 and DT90 values in photolysis test.

	DT50 (days)	DT90 (days)
Irradiated	16.5	57.8
Non-Irradiated	20.7	74.4

It is concluded that the degradation of Ethephon in soil is somewhat enhanced by irradiation. The degradation pathway did not differ between the non-irradiated and the irradiated treatment group.

Photodegradation in air

A theoretical calculation of the photo-oxidation of ethephon in the atmosphere, using the method of Atkinson (1989), updated by Kwok & Atkinson (1995) gave a DT50 value of 10.16 days, assuming 12 hour light per day, suggesting that the concentrations of ethephon in air are likely to be low.

Ethylene, one of the major hydrolysis products of ethephon, is volatile (estimated Henry's Law constant is 1.08 Pa/mol.m^3). The estimated half life time (Atkinson) calculated with EPI-WIN version 3.10 for photodegradation of ethylene is 1.26 days (assuming 12 hour light per day).

4.1.2 Biodegradation

4.1.2.1 Screening tests

Ready biodegradability

Ethephon was not readily biodegradable in a closed bottle test.

4.1.2.2 Simulation tests

Degradation in water/sediment systems

Water/sediment studies were conducted in two water/sediment systems, performed according to Directive 95/36/EC and Part G Section 2.1 (1) of the Dutch Guidelines for the Submission of Applications for Registration of Pesticides. The ratio water : dry weight sediment was 1 : 5.9 for the Manningtree system and 1 : 5.3 for the Ongar system. Prior to testing, the sediments and associated water were acclimated in flasks for approximately four weeks in the dark at 20 ± 2°C. During the acclimatisation and experimental period a continuous flow of moistened air was passed into the flask at a sufficient rate (70 mL/min) to allow aeration and avoiding mixing of water and sediment phases. After application of the test substance, flasks were connected to a system of pumps, scrubbers and moistening units to supply the air-flow. The effluent air was led through a series of four traps. The first trap contained ethylene glycol (for volatiles). The three subsequent traps contained a saturated solution of pyridinium hydrogen bromide per bromide (PHBPB). PHBPB is a source of bromine which reacts with ethylene. In this reaction dibromoethane is formed. The entire system was incubated under dark conditions at 20 ± 2°C. Two flasks were connected with a furnace (800°C, with a copper catalyst), followed by a series of traps, containing KOH solution to trap CO_2 that could be produced by the oxidation of any organic volatile degradate of ethephon. During acclimatisation and the experimental phase, the oxygen content, pH and redox potential of the flasks were determined (approximately once a week).

Table 4.1.2.2-1. Physico-chemical characterisation of water and sediment during acclimatisation and incubation with 14C-Ethephon.

System	Parameter	water	sediment
		range	range
Manningtree	O_2 (% saturation) pH Redox potential (mV)	52 - 77 7.02 - 8.50 +120 - +391	 -395 - -195
Ongar	O_2 (% saturation) pH Redox potential (mV)	48 - 67 7.19 - 8.73 +124 - +320	 -371 - -200

Samples (for analysis) were taken from the flasks at t = 0 and t = 6h and at t = 1, 2, 4, 8, 14 and 30 days after application. Sediment and water were separated by decantation. Simultaneously with the sampling of flasks, traps were also taken for analysis. Traps that were attached to the furnace were changed at 4, 14 and 30 days after application.

Table 4.1.2.2-2 shows the DT50 and DT90 values obtained in these studies. The primary degradation of ethephon is rapid in both systems; ethylene was the major (volatile) radioactive metabolite formed (> 95% after 30 days). Only small quantities were sorbed to the sediment. No major metabolites were found in the sediment. The degradation rate in the whole sediment/water system was similar to that in the water phase alone. The DT50 values corresponded with those found in the hydrolysis experiment, indicating that the route of degradation was abiotic.

Table 4.1.2.2-2. DT50 and DT90 values for ethephon in the water phase and in the total water/ sediment system (calculated by RMS from the results of the main experiment).

	Manningtree system		Ongar system	
	DT50 (d)	DT90(d)	DT50 (d)	DT90(d)
Water phase	2.6	8.5	2.2	7.2
Total water/sediment system	3.0	9.9	2.7	8.6

4.1.3 Summary and discussion of degradation

Degradation in water

Four studies relevant for the assessment of degradation of ethephon are available. In a standard ready biodegradability test ethephon is considered not readily biodegradable.

Ethephon hydrolyses rapidly under neutral and alkaline conditions (t1/2 = 2.5d and 1.4d at pH 7 and 9, respectively), with ethylene and phosphoric acid as the major degradation products formed. Under acidic conditions (pH 5), hydrolysis is much slower (t1/2 =99d). The hydrolysis of ethephon was tested at different pH values (see also Section 4.1.1, Table 4.1.1.-1) showing half-lives at 20°C of 2.5 and 1.4 days for pH 7 and 9, respectively. The half-life for acidic conditions (pH 5) was much lower, i.e. 99.1 days (measured). Based on the available information, ethephon cannot be considered to undergo fast primary degradation in hydrolysis studies (cf. CLP guidance Annex II, Section II.2.3.8).

The available simulation studies in water/sediment do not demonstrate ultimate degradation of the substance in surface water with > 70% degradation in 28 days (cf. CLP guidance Annex II, Section 2.3). The studies confirmed the rapid primary degradation rate of the substance with DT50 system of 2.2 and 2.6 days at pH ≥ 7 with formation of the degradation products ethylene and phosphoric acid. These degradation half-lives obtained in the water/sediment studies are comparable to those obtained in the hydrolysis studies, suggesting that the mechanism of degradation is abiotic. As the water/sediment studies do no provide information on the degradation of ethephon at pH values < 7, it can not be excluded that the primary degradation half-life of ethephon at pH values below 7 in water/sediment studies is longer than 16 days and, as a consequence, it can not be concluded that ethephon undergoes fast primary degradation.

Thus, based on the results from the ready biodegradation study, the hydrolysis study and the two simulation studies it has not been demonstrated that ethephon undergoes fast primary degradation. Furthermore, mineralisation of more than 70% has not been demonstrated. Ethephon cannot, therefore, be regarded as rapidly or readily degradable.

4.2 Environmental distribution

4.2.1 Adsorption/desorption

Both the parent compound ethephon and its metabolite 2-hydroxyethylphosphonic acid (2-HEPA) have a low mobility in soil. Adsorption K_{oc} values of ethephon, in four different types of soil and in one type of sediment, varied between 608 and 4078 L/kg, showing that the mobility of ethephon is low to moderate. In another study the adsorption K_{oc} values of the metabolite 2-hydroxyethylphosphonic acid (2-HEPA) were determined and appeared to vary between 1464 and 12055 L/kg, showing the low mobility of 2-HEPA.

Adsorption of both ethephon and 2-HEPA to soil particles was correlated to organic carbon content of the soil.

4.2.2 Volatilisation

Since the vapour pressure was below the lower detection limit (<10-3 Pa) in the whole temperature range from 18 to 80 °C, ethephon was not considered as a volatile substance.

4.3 Bioaccumulation

4.3.1 Aquatic bioaccumulation

No bioaccumulation studies were performed. Based on the log Kow of ethephon of –1.89 at pH 7 bioaccumulation in the aquatic ecosystem is not expected.

4.3.2 Summary and discussion of bioaccumulation

The log Kow of ethephon (-1.89 at neutral pH) is lower than the criterion for bioaccumulation according to CLP (log Kow >4) and Directive 67/548/EEC (log Kow > 3). Ethephon is therefore considered as substance with limited potential for bioaccumulation.

5 HUMAN HEALTH HAZARD ASSESSMENT

The current proposal is a revision of the current entry in Annex VI to the CLP regulation (29 ATP, 2004). The summaries included in this proposal are partly copied from the Draft Assessment Report and Proposed Decision of the Netherlands prepared in the context of the possible inclusion of the active substance ethephon in Annex I of Council Directive 91/414/EEC (revised DAR (January 2006), revised addendum (January 2006), ARfD addendum (October 2006) and ARfD addendum 2 (June 2008)). Some details of the summaries were not included when considered not important for a decision on the classification and labelling of this substance. For more details the reader is referred to the DAR. No references to individual mammalian studies are included to protect the privacy and integrity of the individual (Article 14 of directive 91/414). These references are available in the DAR.

Ethephon was also discussed in the TC-C&L in November 2006 (Summary record ECB/20/07). The conclusions of this discussion can be found in Annex 1. To provide an overall view of the substance, we have also included information related to the hazard classes that do not need to be changed. Information related to acute toxicity and sensitisation results in a classification proposal that differs from the current classification. Information regarding the other toxicological endpoints should be regarded as additional.

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

The absorption, distribution, metabolism and excretion of 14C-ethephon in rat was investigated after a single intravenous dose of 50 mg/kg bw, a single oral dose of 50 and 1000 mg/kg/bw, and a single oral dose of 50 mg/kg bw after 14 daily pretreatments at the same dose. In addition, metabolism was studied after a single gavage dose of 50 mg/kg bw in rats.

Absorption

Based on RA recovered from urine, expired air/volatiles, cage wash, tissues and residual carcass (hence excluding RA recovered from faeces), absorption 120 hours after administration in rats was 78-84% AR, irrespective of sex and oral dosing regime.

Distribution

Tissue concentrations in male and female rats of the same treatment group were comparable. There were no remarkable differences between tissue concentrations of rats after treatment with a single or repeated oral dose of 50 mg/kg bw. Tissue concentrations were highest in liver, followed by blood, kidney, bone, spleen, lungs and heart. After treatment with a single oral dose of 1000 mg/kg bw, tissue concentrations were highest in bone, followed by kidney, liver, blood, spleen and lungs.

After treatment with a single intravenous dose of 50 mg/kg bw, tissue concentrations in bone and kidney were slightly higher than in rats given a single oral dose of 50 mg/kg bw, and in blood and liver slightly lower, whilst concentrations in other tissues and organs of intravenously treated rats were comparable to those of orally dosed animals. Overall retention of radioactivity in tissues and organs of intravenously treated rats was comparable to that of animals given a single oral dose.

Metabolism

In one study, the fraction containing the disodium salt of ethephon was the major component in urine and faeces, representing on average 84-87% and 47-59%, respectively, of the total radioactivity in the samples of urine and faeces which were chromatographed. Fractions other than that containing the disodium salt of ethephon individually accounted for ≤6.0% AR. Definitive identification of other compounds in urine besides the disodium salt of ethephon was

not successful. Confirmation of identity of compounds in faeces samples was not attempted due to the low levels of radioactivity present.

Investigations into the metabolism of ethephon by TLC and HPLC revealed the presence of parent compound (ethephon) in the kidneys and liver of male rats as the major radioactive component. The new experimental procedures revealed the presence of metabolite 2-hydroxyethephon (HEPA) in the kidneys and liver although at much lower levels than parent.

Excretion

Excretion was essentially complete within the first 24 hours after dose administration, when the amount of AR excreted represented 94-99% of that excreted after 120 hours.

Initial absorption of 14C-ethephon by rats given a single oral dose of 50 mg/kg bw was faster than of rats given a single oral dose of 1000 mg/kg bw (Tmax 1.0-1.3 and 1.9-2.5 hours respectively), but elimination half-life was much shorter at 1000 mg/kg bw than at 50 mg/kg bw (4.1-9.0 versus 30-304 hours), resulting in comparable values for overall systemic exposure at 50 and 1000 mg/kg bw (AUC 341-443 and 498-611 mg eq·h/kg, respectively).

There were no remarkable differences between patterns of absorption and excretion of sexes and oral dosing regimes.

5.2 Acute toxicity

5.2.1 Acute toxicity: oral

One oral toxicity study was available, which was in accordance with OECD 401. Single doses of 1.25, 2.50 and 5 ml ethephon base 250/kg bw in males and 1.25, 1.77 and 2.50 ml/kg bw in females were given by gavage to Hilltop-Wistar rats.

5/5 males given 5 ml/kg bw and 2/5 males given 2.5 ml/kg bw/day were found dead within 1 day after treatment. 5/5 females given 2.5 ml/kg bw and 4/5 females given 1.77 ml/kg bw were found dead within 1 day after treatment. Sluggishness, prostration, piloerection and/or emaciation was observed in males given 5 or 2.5 ml/kg bw and females given 2.5 or 1.77 ml/kg bw. A decrease in body weight gain was noted among the surviving males given 2.5 ml/kg bw and in the surviving female given 1.77 ml/kg bw. At macroscopic post mortem examination mottled, tan, brown and/or green liver, black stomach and/or dark red lungs were noted among animals found dead during the study. Based on the density of 1.39 g/ml of ethephon base 250, and a purity of 70.75% ethephon, the acute oral LD50 of ethephon Base 250 was calculated to be 3030 mg/kg bw for both sexes combined (LD50 males 3730 mg/kg bw, LD50 females 2210 mg/kg bw). Corrected for the pure active substance, this results in an acute oral LD50 of ethephon of 2144 mg/kg bw for both sexes combined (LD50 males 2639 mg/kg bw, LD50 females 1564 mg/kg bw).

Table 5.2.1-1 Acute toxicity, LD50 values

Test substance	LD_{50} ethephon Base 250	LD_{50} ethephon	Species	Vehicle
Ethephon Base 250, RTS 3830AA, purity 70.75%	3730 mg/kg bw in males 2210 mg/kg bw in females	2639 mg/kg bw in males 1564 mg/kg bw in females	Rat	Distilled water

In addition, an acute oral neurotoxicity study (according to OECD guideline 424) was performed. After single administration of 0, 500, 1000 and 2000 mg/kg bw ethephon base 250 by gavage to Sprague Dawley rats (12/sex/dose), one female at 1000 mg/kg bw was found

dead on day 5 and two females dosed at 2000 mg/kg bw died within day 2 days after dosing. Body weight was significantly reduced for males at 2000 mg/kg bw on day 7; a slight reduction of body weight was also noted on day 7, for females at 2000 mg/kg bw. Food consumption was significantly reduced for females at 1000 -or 2000 mg/kg bw in week 1; a slightly reduced food consumption was also noted in week 1 for males at 2000 mg/kg bw.

An increased incidence of pinpoint pupils was noted at all doses on day 0: 10/12 females at 2000 mg/kg bw, 5/12 females each in the 500 and 1000 mg/kg bw groups, 6/12 males in the 2000 mg/kg group, 3/12 males each in the 500 and 1000 mg/kg bw groups (compared to 1/12 female control and 1/12 male controls); the myosis persisted up to day 14 in a few treated animals. The body temperature of the 2000 mg/kg bw group females was significantly decreased on day 0. A statistically significant increase in urination was noted for males at 2000 mg/kg bw on day 0, when compared to control males. Reduced motor activity was noted for males given 1000 and 2000 mg/kg bw and females 2000 mg/kg bw on day 0. Macroscopic post mortem examination and histopathological examination of nervous tissues did not reveal any abnormalities. No effects on brain weight, length and width were noted.

The dose-related increase in the incidence of myosis (at all doses), increased urination (at 2000 mg/kg bw), and reduced motor activity (at 1000 and 2000 mg/kg bw) on day 0 are considered to be indicative of neurotoxicity and consistent with acetylcholinesterase inhibition. Based on the increased incidence of myosis, a NOAEL of < 500 mg/kg bw was set.

5.2.2 Acute toxicity: inhalation

One inhalation toxicity study was available, which was in accordance with OECD 403. Sprague-Dawley rats were dosed with 2.11 ± 0.22, 3.34 ± 0.41 and 6.12 ± 0.66 mg ethephon base 250/L (actual doses) for 4 hours (whole body exposure). The MMAD ± GDS was 3.3-3.4 ± 3.4-4.2, 4.9-5.0 ± 3.4-4.4 and 5.8-6.0 ± 4.0-4.1 µm, respectively.

5/5 males and 5/5 females given 6.12 mg/L were found dead on day 1 of the study. Hypothermia and tremors were noted in animals given 6.12 mg/L, wet fur, blepharospasm, perioral and perinasal wetness, periocular, perioral and perinasal encrustation, bright red extremities, audible respiration, mouth breathing. A slow surface-righting reflex and/or an absent tail pinch reflex were noted among animals given 6.12 and 3.34 mg/L. Animals given 2.11 mg/L showed wet fur, perioral and periocular encrustation, bright red extremities and audible respiration. A decreased body weight gain was noted among animals given 3.34 mg/L. At macroscopic post-mortem examination unkempt fur, discoloration of lungs, liver, salivary glands and thymic region, brain haemorrhage and/or gaseous stomach and intestines were noted among the animals found dead during the study. No test substance related findings were noted. The acute LC50 of ethephon base 250 was found to be 4.52 mg/L for both male and female rats. Corrected for the pure active substance (purity ethephon base 250 72.2%), this results in an acute oral LC50 of ethephon of 3.26 mg/L.

Table 5.2.2-1 Acute toxicity, LC50 values

Test substance	LC50 ethephon Base 250	LC50 ethephon	Species	Vehicle
Ethephon Base 250, BRRC sample number 52-226, purity 72.2%	4.52 mg/L	3.26 mg/L	Rat	none

5.2.3 Acute toxicity: dermal

One dermal toxicity study was available, which was in accordance with OECD 402. New Zealand White rabbits were exposed for 24 hours to single doses of 0.5, 1.0 or 2.0 ml ethephon base 250/kg bw, under occlusion.

5/5 males and 5/5 females given 2.0 ml/kg bw were found dead within 1 day after the start of treatment. 1/5 males and 2/5 females given 1.0 ml/kg bw were found dead within 3 days after the start of treatment. One female given 0.5 ml/kg bw was killed in extremis, due to injury during restraint. Pinpoint pupils and salivation was observed in males given 2 ml/kg bw, unsteady gait, prostration in males and females given 1.0 ml kg/bw. Erythema and/or necrosis was noted in all treated animals. A decreased body weight gain was shown by surviving animals given 1 ml/kg bw. At macroscopic post mortem examination dark red lungs and/or trachea, mottled livers and/or intestines filled with paste-like faecal material were noted among all treated animals. The acute dermal LD50 of ethephon Base 250 was found to be 1.12 ml/kg bw for both sexes combined (LD50 males 1.23 ml/kg bw, LD50 females 1.00 ml/kg bw). Based on the density of 1.39 g/ml of ethephon Base 250, the acute dermal LD50 of ethephon Base 250 was calculated to be 1560 mg/kg bw for both sexes combined (LD50 males 1710 mg/kg bw, LD50 females 1390 mg/kg bw). Corrected for the pure active substance (purity ethephon base 250 70.75%), this results in an acute oral LD50 of ethephon of 1104 mg/kg bw for both sexes combined (LD50 males 1210 mg/kg bw, LD50 females 983 mg/kg bw).

Table 5.2.3-1 Acute toxicity, LD50 values

Test substance	LD50 ethephon Base 250	LD50 ethephon	Species	Vehicle
Ethephon Base 250, RTS 3830AA, purity 70.75%	1710 mg/kg bw in males 1390 mg/kg bw in females	1210 mg/kg bw in males 983 mg/kg bw in females	Rabbit	none

5.2.4 Acute toxicity: other routes

No data available.

5.2.5 Summary and discussion of acute toxicity

Oral, inhalation and dermal LD50 or LC50 values in rats or rabbits were 1564 mg/kg bw, 3.26 mg/L and 983 mg/kg bw, respectively. Although in the acute oral neurotoxicity study only 2/12 females died after administration of a dose of 2000 mg/kg bw (without correction), the data in this study were considered less relevant than the acute toxicity study. It could be argued that the classification of ethephon for acute dermal toxicity and corrosivity is a double classification based on the same effect and therefore not warranted. Although the mechanism of toxicity in the dermal study possibly is corrosivity, it cannot be excluded that at least part of the effects are unrelated to the corrosive properties. Therefore, the substance should be classified for acute dermal toxicity as proposed, based on the LD50 in females. Also, no classification for acute dermal toxicity for corrosive substances would be inconsistent with existing harmonized classifications as many corrosive substances in Annex VI are also classified for acute dermal toxicity. Some even in a more severe category such as R24. This means that the classification for acute dermal toxicity provides additional information to the user. Therefore, classification for skin corrosivity and acute dermal toxicity is required.

Therefore, according to 67/548/EEC, ethephon should be classified as Xn; R20/R21/R22 because the LC50 is within the limits of 1 - 5 mg/L, the oral LD50 is within the limits of 200 - 2000 mg/kg bw and the dermal LD50 is within the limits of 400 – 2000 mg/kg bw. According to EC 1272/2008, ethephon should be classified as Cat 4; H302 (limits 300 – 2000 mg/kg bw, oral), Cat 3; H311 (limits 200 – 1000 mg/kg bw, dermal) and Cat 4; H332 (limits aerosol 1 – 5 mg/L).

In addition, in the acute inhalation study, rats given 2.11 and 6.12 mg/L ethephon base 250 (~ 1.49 and 4.32 mg/L ethephon) showed audible respiration. This indicates respiratory tract irritation. Based on this study and following the current classification, a specific concentration limit is advised according to DSD: Xi; R37: 5% ≤ C < 10% (and C; R34: C ≥ 10%, see 5.4). According to the criteria of EC 1272/2008, additional labelling with EUH071 is proposed (see Annex I 3.1.2.3.3 and footnote 1 to table 3.1.3, Annex II 1.2.6, CLP Guidance 3.1.4.2) as there were effects on the lungs in the inhalation study, the corrosivity to the skin and the acidic nature (pH=1.6). Since ethephon is classified as corrosive (see paragraph 5.4), and labeled as corrosive to the respiratory tract this implicitly covers the potential to cause RTI and additional classification STOT SE 3; H335 is considered superfluous. As a consequence an SCL for STOT SE 3 H335 is not required as the classification as corrosive applies to mixtures at 5% and above. We therefore propose to remove the current concentration limit.

The SCL for STOT SE 3 H335 was probably based on a translation of the SCL between 5 and 10% for R37 plus correction for the lower GCL 5% for corrosive substances.

The classification of ethephon was discussed by the TC-C&L in November 2006. The TC-C&L agreed with the proposed classification for Xn; R20/21/22 and with the specific concentration limit for respiratory tract irritation.

5.3 Irritation (additional information)

5.3.1 Skin

A skin irritation/corrosion study was performed. The study was not performed in accordance with OECD 404. Ethephon has a pH of 1.6, therefore, a skin irritation study should not be performed, or should have been initiated with one animal. Furthermore, the study was not performed under GLP conditions, and the description of the study design and results was rather limited. In addition, six rabbits per application period were used instead of three animals (or one animal). However, considering the results of the test (see conclusions), the study is considered acceptable.

Six rabbits (3 males, 3 females) were treated with 0.5 ml ethephon base 250 for 4 hours, and readings were made at 5, 24 and 48 hours after the initiation of the exposure. In addition, six rabbits (3 males, 3 females) were treated with 0.5 ml ethephon base 250 for 1 hour, and readings were made at 5, 24 and 48 hours after initiation of the exposure. Necrosis was observed after 4 hours of test substance application. Since the study was terminated after the 48 hours observation, it is not clear whether or not full thickness destruction would have occurred.

Table 5.3.1-1: Results skin irritation study

	4 hours application			1 hour application		
Scores observed after	5 hours	24 hours	48 hours	5 hours	24 hours	48 hours

	4 hours application			1 hour application		
Scores observed after	5 hours	24 hours	48 hours	5 hours	24 hours	48 hours
Erythema1	0,1,0,0,2,2 (0.8)2	1,2,2,2,2,2 (1.8)	2,2,2,2,2,2 (2)	0,0,1,1,0,1 (0.5)	0,0,2,2,1,2 (1.2)	0,1,2,2,2,2 (1.5)
Oedema	0,0,4,3,0,2 (1.5)	0,1,4,3,0,2 (1.7)	0,2,3,2,0,2 (1.5)	0,0,0,0,0,0 (0)	0,0,0,0,0,0 (0)	0,0,0,0,0,0 (0)
Necrosis	-,n, n, n,-,n	-,n, n, n,-,n	-,n, n, n,-,n	-,-,-,-,-,-	-,-,-,-,-,-	-,-,-,-,-,-

n : necrosis

- : no necrosis observed

1 : readings for erythema were made around the areas of necrosis

2 : mean score between brackets

5.3.2 Eye

No eye irritation study with Ethephon was performed, due to the pH of 1.6

5.3.3 Summary and discussion of irritation

According to the criteria of Directive 67/548/EEC, ethephon should be classified with C; R34 because of the observed necrosis in the skin irritation study. No eye irritation study with ethephon was performed, due to the pH of 1.6. ethephon should be classified as "Risk of serious damage to eyes". However, because ethephon is classified as corrosive, the risk of severe damage to eyes is considered implicit and no additional risk phrase for ocular lesion is assigned. Furthermore, the effects observed in the acute inhalation study indicate respiratory tract irritation.

According to the criteria of EC 1272/2008, ethephon should be classified with Skin Corr1C; H314. In addition, an SCL for R36/37/38 should be applied for a concentration between 5 and 10%.

5.4 Corrosivity (additional information)

Based on the low pH of ethephon (1.6) and the results of the skin irritation study (which should not have been performed due to the low pH), it can be concluded that ethephon is corrosive. Therefore, ethephon should be classified with R34 according to the criteria of Directive 67/548/EEC. Since necrosis was only observed after a 4 hour exposure period and not after a 1 hour period, ethephon should be classified as Skin Corr1C; H314 according to the criteria of EC 1272/2008. In addition, an SCL for R36/37/38 should be applied for a concentration between 5 and 10%. Further, an additional labelling with EUH071 is proposed as described in paragraph 5.2.5. Due to the classification as corrosive (and labelling for

respiratory corrosivity) this implicitly covers the potential to cause RTI and an SCL for STOTSE 3; H335 at and above 5% under CLP is considered superfluous.

No SCL for Skin Corr 1C is needed as the current SCL of 10% for R34 is a generic concentration limit included because all concentration limits were included at that time in the entry in Annex I of DSD.

The classification of ethephon was discussed by the TC-C&L in November 2006. The TC-C&L did not propose changes in classification (C; R34, with an SCL of 5-10% for R36/37/38).

5.5 Sensitisation (additional information)

5.5.1 Skin

A Local Lymph Node Assay was performed with ethephon (AE F016382 00 TK71 A101) in female mice, partly in accordance with OECD 429. Due to its corrosive pH, the solution of test item in water was adjusted to pH 4.5 (±0.5) using aqueous sodium hydroxide (10M). Actual doses of 3.6, 7.1, 17.9, and 35.7% were applied to the dorsum of each ear, once daily for 3 consecutive days. Positive and negative controls were included. No cutaneous reactions were observed at the treated sites of any of the animals (controls and test). Negative lymphoproliferative responses (SI<3) were noted for ethephon at all concentrations tested. Since the influence of adjusting the pH of ethephon is not properly addressed, no conclusions regarding the skin sensitising properties of ethephon can be drawn from this study.

In addition, a Buehler test was performed with BASE A-250, lot no. 4022193, in Hartley guinea pigs, according to OECD guideline 406, with the exception that five animals per sex were used for the treatment group, instead of a total of 20/group. Doses of 25% w/v in distilled water were used for induction (3 topical inductions, for 6h under occlusion) and 10% w/v for the challenge.

Topical induction with 25% w/v caused no dermal responses in any of the three inductions, with the exception of two animals, which showed slight patchy erythema, one after the second induction and one after the third induction. Following challenge with 10% w/v, slight patchy erythema was noted after 24 hours in all animals of the treatment group and in 7 of 10 animals of the negative control animals. After 48 hours, 4 animals of the treatment group and one animal of the negative control group showed slight patchy erythema.

A maximisation study was performed in accordance with OECD 406. Guinea pigs (10 controls (5/sex), 20 test animals (10/sex)) were treated with ethephon (purity 74.1%); 0.5% w/w for intradermal induction, or 50% w/w topical induction. 25% was used for the topical challenge (occlusive, 24 h). Results of the induction phase were not included in the study report. Eight (out of twenty) experimental animals reacted positive to the challenge phase, versus none of the controls. It is however not clear whether these findings can be interpreted as a sensitisation reaction or whether they are the result of the low pH of the test substance.

5.5.2 Respiratory system

No data available.

5.5.3 Summary and discussion of sensitisation

Ethephon does not have sensitising properties in a Buehler test or in an LLNA test. However, both tests were of limited value since the Buehler test was performed with far too less animals, and the experience of the LLNA test was insufficient to assess the effect of altering the pH before the test, and the influence on the results is unclear. Eight out of twenty experimental animals (40%) in the maximisation study reacted positive to the challenge phase. It is

however not clear whether these findings can be interpreted as a sensitisation reaction or whether they are the result of the low pH of the test substance. Overall, ethephon should not be classified for sensitisation.

The classification of ethephon was discussed by the TC-C&L in November 2006. The TC-C&L did not propose changes in classification and agreed not to classify ethephon for sensitisation.

5.6 Repeated dose toxicity (additional information)

5.6.1 Repeated dose toxicity: oral

The results of the relevant subacute, subchronic and chronic oral toxicity studies with ethephon are summarized in Table 5.6.1-1.

Table 5.6.1-1: Summary of repeated dose oral toxicity data

Route/Test material	Duration Method/ Guideline	Species/ strain/ sex/ no. per group	Dose levels/ frequency of dosing	effects	LOAEL (mg/kg bw/d)	NOAEL (mg/kg bw/d)
Diet, range finding study* Ethephon Base a-250, lot no. 62833 Purity: 71.14%	14 days No OECD	Dog, Beagle, 1/sex/dose	0, 1, 3, 10, 30, 100, 300, 1000, 3000, 10000 mg/kg food (~ 0, 0.05, 0.15, 0.5, 1.5, 5, 15, 50, 150 and 500 mg/kg bw/day), corrected for purity	significant inhibition in brain ChE activity (> 20%) in females at doses ≥ 1000 mg/kg food	50 mg/kg bw/day	na
Diet, range finding study Ethephon Base a-250, lot A51563 Purity: 71.3%	28 days partly in accordance with OECD 407	Rat, Sprague-Dawley CD 10/sex/dose	Males: 0, 52, 106, 214, 431, and 831 mg/kg bw/day; females: 0, 59, 119, 251, 487 and 980 mg/kg bw/day, corrected for purity	In males, ≥ 106 mg/kg bw/day: reduced plasma ChE activity (27-35%); reduced erythrocyte ChE activity (22-73%) In females, ≥ 59 mg/kg bw/day: reduced plasma ChE activity (29-63%); ≥ 119 mg/kg bw/day: reduced erythrocyte ChE activity (35-78%)	106 mg/kg bw/day	52 mg/kg bw/day
Diet,	28 days	Rat,	Males: 0,	Top dose: loose	962	-

Route/Test material	Duration Method/ Guideline	Species/ strain/ sex/ no. per group	Dose levels/ frequency of dosing	effects	LOAEL (mg/kg bw/d)	NOAEL (mg/kg bw/d)
range finding study* Ethephon Base a-250, lot A51563 Purity: 71.3%	No OECD	Sprague-Dawley CD 15/sex/ dose	962, 2299, 4673 mg/kg bw/day; females: 0, 996, 2488 and 4905 mg/kg bw/day, corrected for purity	faeces from day 10. Significantly reduced body weight: at top dose (27% and 34% for males and females), mid dose (15% and 18% for males and females) and low dose (18% in females); at ≥ mid dose in males and ≥ low dose in females: reduced food consumption (not observed every week). Dose-related inhibition of ChE activity in plasma (week 2, males: 23, 31 and 42%, females 66, 66 and 74%, at week 4, males: 27, 34 and 45%, females: 46, 58 and 61%) and erythrocytes (week 2, males: 69, 84 and 91%, females 72, 82 and 91%, at week 4, males: 72, 82 and 91%, females: 73, 80 and 89%) Statistically significant inhibition of brain ChE activity in males and females at 50000 mg/kg food (15% and 13%) after 2 weeks. Decreased absolute weights of heart and lungs in males and females at top dose; increased relative weights of liver and brain in males and females at top dose;	mg/k bw/day	

Route/Test material	Duration Method / Guideline	Species/ strain/ sex/ no. per group	Dose levels/ frequency of dosing	effects	LOAEL (mg/kg bw/d)	NOAEL (mg/kg bw/d)
				increased relative kidney weights in females at mid and top dose. Significantly lower absolute spleen weights at all doses in males and mid and high dose in females.		
Diet, range finding study Ethephon Base a-250, lot A51563 Purity: 71.3%	28 days partly in accordance with OECD 407	mouse, Charles River CD-1 10/sex/ dose	Males: 0, 5.3, 18, 51, 181 and 546 mg/kg bw/day; females: 0, 6.5, 22, 69, 209 and 635 mg/kg bw/day, corrected for purity	At 4 weeks: ≥ 300 mg/kg food: reduction of ChE activity in plasma (22-63%); ≥ 1000 mg/kg food: reduction of ChE activity in erythrocytes (34-62%) At 2 weeks: inhibited plasma and erythrocytes ChE activity in females at 300 and 1000 mg/kg food, and in males at 1000 mg/kg food	69 mg/kg bw/day	22 mg/kg bw/day
Diet, range finding study* Ethephon Base a-250, lot A51563 Purity: 71.3%	28 days No OECD	mouse, Charles River CD-1 15/sex/ dose	Males: 0, 525, 1815, 4780 and 10212 mg/kg bw/day; females: 0, 632, 2231, 5852 and 14945 mg/kg bw/day, corrected for purity	At the top dose: significantly reduced food consumption in males and females. Weight loss in males and females at the top dose in week 1, followed by weight gains in subsequent treatment weeks. Significantly lower total body weight gains in males and females at 25000 mg/kg food (56% and 47% compared to controls). Dose-related inhibition of ChE activity in plasma (week 2, males: 55,	525 mg/kg bw/day	-

Route/Test material	Duration Method / Guideline	Species/ strain/ sex/ no. per group	Dose levels/ frequency of dosing	effects	LOAEL (mg/kg bw/d)	NOAEL (mg/kg bw/d)
				54, 77 and 74%, females 55, 66, 80 and 82%; at week 4, males: 55, 60, 71 and 77%, females: 57, 65, 73 and 78%) and erythrocytes (week 2, males: 54, 68, 88 and 90%, females 62, 80, 88 and 92%; at week 4, males: 57, 67, 82 and 87%, females: 62, 76, 82 and 89%). Dose-related inhibition of ChE activity in brain was noted after 4 weeks among males at 10000, 25000 and 50000 mg/kg food (12%, 14%, and 19%, respectively). Increased relative brain, kidneys and lung weights and decreased absolute spleen and heart weights among males at 50000 mg/kg food. Decreased absolute and relative (to body and brain) weights of the spleen among females at 50000 mg/kg food.		
Diet Ethephon Base 250, batch no. 2250197 Purity: 71.3%	28 days No OECD	Dog, Beagle, 3 females /dose	0, 250, 750 mg/kg food, equal to 0, 6, 14 mg/kg bw/day, equal to 0, 4.3 and 10 mg pure ethephon/kg bw/day	Decreased erythrocyte acetylcholinesterase activity at 14 mg/kg bw; Decreased erythrocyte acetylcholinesterase activity at all dose levels	14 mg/kg bw/day	6 mg/kg bw/day

Route/Test material	Duration Method / Guideline	Species/ strain/ sex/ no. per group	Dose levels/ frequency of dosing	effects	LOAEL (mg/kg bw/d)	NOAEL (mg/kg bw/d)
Diet* Ethephon Base 250, lot no. A62833 Purity: 71.14%	1 year OECD 409	dog, Beagle 5/sex/dose	Males: 0, 2.79, 8.11, 27.37 and 54.17 mg/kg bw/day; females: 0, 2.55, 8.38, 29.71 and 49.96 mg/kg bw/day, corrected for purity.	Decreased total body weight gain in males and females top dose group (mean weight gain deficit relative to controls 0.4 kg and 0.5 kg in males and females, respectively). Decreased absolute spleen weight among males top dose (55% compared to control values). Decreased relative spleen weight in males and females top dose (69 and 75% when compared to control values, respectively). Decreased absolute thyroid weight (66% when compared to control values) and absolute heart weight in males top dose		na
Diet, combined toxicity/carcinogenicity study Industrial Base 250, ethephon Purity: 70.6-72.1%	2 years OECD guideline 453, 1981	Rat, Sprague-Dawley CD 90-100/sex/dose	Males: 0, 13, 131, 446 and 1416 mg/kg bw/day; females: 0, 16, 161, 543 and 1794 mg/kg bw/day, corrected for purity.	Increased incidence of loose (semi-solid) faeces in males at 30000 mg/kg food. Increased incidence of red and thickened ears in females at 3000 ppm or higher, with a dose-related trend. Significantly lower body weights in males and females at 30000 ppm throughout treatment; (at the end of the first year (relative to untreated controls) 17% and 27% for males and females at 30000 ppm, respectively). Food consumption	131 mg/kg bw/day	13 mg/kg bw/day

Route/Test material	Duration Method / Guideline	Species/ strain/ sex/ no. per group	Dose levels/ frequency of dosing	effects	LOAEL (mg/kg bw/d)	NOAEL (mg/kg bw/d)
				was significantly reduced in males and females at 30000 mg/kg food in the majority of measurement periods in the first year of treatment. Dose-dependent inhibition of plasma and erythrocyte ChE activities at all dose levels: in plasma from males, the inhibition ranged from 17-44, 27-47, 38-67 and 45-56% at 300, 3000, 10000 and 30000 ppm, respectively, and in plasma from females from 15-27, 37-59, 47-65 and 56-72% at 300, 3000, 10000 and 30000 ppm, respectively; in erythrocytes from males, the inhibition ranged from 4-10, 39-47, 65-81 and 83-87% at 300, 3000, 10000 and 30000 ppm, respectively, and in erythrocytes from females from 9-19, 43-63, 72-79, and 82-86% at 300, 3000, 10000 and 30000 ppm, respectively. Serum glucose significantly lower for males and females at 30000 ppm after 26 weeks, and for males at 30000 ppm after 52 weeks. Serum phosphorus significantly reduced for males at 30000		

Route/Test material	Duration Method / Guideline	Species/ strain/ sex/ no. per group	Dose levels/ frequency of dosing	effects	LOAEL (mg/kg bw/d)	NOAEL (mg/kg bw/d)
				ppm after 13 and 26 weeks. Slight perturbations in red blood cell parameters for males at 30000 ppm at several time points (erythrocyte counts and haematocrit increased, and MCHC decreased. Prothrombin time lower for females at 30000 ppm. Urinary pH significantly lower throughout the study for males and females at 10000 and 30000 ppm. Significantly lower urinary pH for females at 300 ppm after 103 weeks and for females at 3000 ppm after 77 and 103 weeks. Specific gravity of urine significantly higher for females at 10000 ppm and 30000 ppm after 50 and 77 weeks. Increased relative kidney weights for males and females at 30000 ppm (52 weeks). At terminal sacrifice, relative kidney weights were significantly higher for males at 3000 and 10000 ppm, and for males and females at 30000 ppm. In the kidneys, the incidence of glomerulosclerosis was significantly increased in females at 30000 mg/kg food at terminal sacrifice.		

Route/Test material	Duration Method/ Guideline	Species/ strain/ sex/ no. per group	Dose levels/ frequency of dosing	effects	LOAEL (mg/kg bw/d)	NOAEL (mg/kg bw/d)
				In the liver, the incidence of biliary hyperplasia was significantly higher in males at 30000 mg/kg food at terminal sacrifice.		
Dietary carcinogenicity study Industrial Base 250, ethephon Purity: 70.6-72.0%	78-week OECD guideline 451	Mouse, not specified 70/sex/ dose	Males: 14, 139 and 1477 mg/kg bw/day; females: 17, 173 and 1782 mg/kg bw/day, corrected for purity.	Significantly lower body weights and body weight gains in females at 10000 ppm. The urinary pH was significantly lower in males at 1000 and 10000 ppm after 77 weeks. Inhibited plasma ChE activity (35-41 and 65-71% in the 1000 and 10000 ppm male dose groups, respectively, and 18-24, 41-61, and 74-76% in the 100, 1000, and 10000 ppm female dose groups, respectively). Inhibited erythrocyte ChE activity (35-36 and 70-72% in the 1000 and 10000 ppm male dose groups, respectively, and 21-36 and 60-74% in the 1000 and 10000 ppm female dose groups, respectively). Brain ChE activity was inhibited by 18% in females at 10000 ppm after 52 weeks.	139 mg/kg bw/day	14 mg/kg bw/day

Critical effects are presented in bold
*supportive study only
na: not applicable

A 14 day range finding study for chronic toxicity was performed in dogs, with doses of 0, 1, 3, 10, 30, 100, 300, 1000, 3000, 10000 mg/kg food. With regard to brain ChE inhibition, the

results of this study indicated a significant inhibition (> 20%) in females from a dose level of 1000 ppm onwards.

In a 28 days range finding study for chronic toxicity doses of 0, 625, 1250, 2500, 5000 and 10000 mg/kg food (nominal), equivalent to 0, 52, 106, 214, 431, and 831 mg/kg bw/day in males and 0, 59, 119, 251, 487 and 980 mg/kg bw/day in females were tested in rats (partly according to OECD 407). Acetone was used as vehicle. Haematology investigations and clinical biochemistry were performed only in the 0, 2500 and 10000 mg/kg food groups. Only a few organs (spleen, heart, lung/bronchi, brain, liver, kidneys) were weighed. No histopathology, ophthalmoscopy and FOB were performed. No analyses for concentration verification in the food were made. Five additional animals/sex were included in the 0, 1250 and 2500 mg/kg food groups, which were used for plasma, erythrocyte and brain ChE determination at day 14. No toxicologically relevant effects on mortality, clinical observations, food consumption, body weight and body weight gain, haematology or liver function were observed. In males, a biologically significant inhibition (> 20%) of ChE activity in plasma (27-35%) and erythrocytes (22-73%) was noted after 4 weeks from 1250 mg/kg food onwards. In females, a dose-related, biologically significant inhibition (> 20%) of ChE activity in plasma (29-63%) at all dose levels and in erythrocytes (35-78%) from 1250 mg/kg food onwards was noted after 4 weeks. No effect on brain ChE activity was observed.

In a 28 days range finding study for chronic toxicity doses of 0, 10000, 25000 and 50000 mg/kg food (nominal), equivalent to 0, 962, 2299, 4673 mg/kg bw/day in males and 0, 996, 2488 and 4905 mg/kg bw/day in females were tested in rats (not according to OECD 407 guideline of 1981 and 1995). Acetone was used as vehicle. No haematology investigations and histopathology were performed. Clinical biochemistry was limited to AchE determination in plasma, erythrocytes and brain. No ophthalmoscopy and FOB were performed. No analyses for the stability, homogeneity and concentrations of the test substance in acetone and diet were performed. However, test substance analyses in acetone and diet in the chronic study in rats (van Miller, 1989) indicated an adequate homogeneity, accuracy and stability of the test substance in acetone and diet. No mortality was observed. Clinical observations showed loose faeces in males and females (top dose) from day 10. Food consumption was significantly reduced for males and for females. Significantly lower body weights were recorded for males and females, leading to total weight gain deficits relative to controls of 27% and 34% for males and females at the top dose 15% and 18% for males and females at the mid dose and 18% for females at the low dose. Dose-related inhibition of ChE activity in plasma (23-74%) and erythrocytes (69-91%) was noted in both sexes after 2 and 4 weeks for all doses. Statistically significant inhibition of brain ChE activity was noted in males and females at the top dose (15% and 13%, respectively) after 2 weeks. Absolute weights of heart and lungs were decreased in males and females, relative weights of liver and brain were increased in males and females, and relative kidney weights were increased in females. Significantly lower absolute spleen weights were recorded for males and females.

In a 28 days range finding study for chronic toxicity doses of 0, 30, 100, 300, 1000 and 3000 mg/kg food (nominal), equivalent to 0, 5.3, 18, 51, 181 and 546 mg/kg bw/day in males and 0, 6.5, 22, 69, 209 and 635 mg/kg bw/day in females were tested in mice (partly according to OECD 407). Acetone was used as vehicle. Haematology investigations and clinical biochemistry were performed only in the 0, 300 and 3000 g/kg food groups. Only a few organs (spleen, heart, lung, brain, liver, kidneys) were weighed. No histopathology, ophthalmoscopy and FOB were performed. No analyses for concentration verification in the food were made. Five additional animals/sex were included in the 0, 300 and 1000 mg/kg food groups, which were used for plasma, erythrocyte and brain ChE determination at day 14. No toxicologically relevant effects on mortality, clinical observations, food consumption, body weight, haematology or liver function were observed. At 4 weeks both sexes showed a biologically and statistically significant inhibition (> 20%) of ChE activity in plasma (22-63%) from 300 mg/kg food onwards and in erythrocytes (34-62%) from 1000 mg/kg food onwards. At 2 weeks the ChE inhibition was more pronounced with biologically significant inhibition in plasma and erythrocytes in females at 300 and 1000 mg/kg food, and in males at 1000 mg/kg food (other dose levels not measured). No effect on brain ChE activity was observed.

In a 28 days range finding study for chronic toxicity doses of 0, 3000, 10000, 25000 and 50000 mg/kg food (nominal), equivalent to 0, 525, 1815, 4780 and 10212 mg/kg bw/day in males and 0, 632, 2231, 5852 and 14945 mg/kg bw/day in females were tested in mice (not according to OECD 407 guideline of 1981 and 1995). Acetone was used as vehicle. No haematology investigations and histopathology were performed. Clinical biochemistry was limited to AchE determination in plasma, erythrocytes and brain. No ophthalmoscopy and FOB were performed. No analyses for the stability, homogeneity and concentrations of the test substance in acetone and diet were performed. However, test substance analyses in acetone and diet in the chronic study in mice (van Miller, 1988) indicated an adequate homogeneity, accuracy and stability of the test substance in acetone and diet. No treatment-related mortality was observed. Food consumption was significantly reduced for males and females at the top dose. Weight loss was observed for males and females at the top dose in week 1, followed by weight gains in subsequent treatment weeks. Significantly lower total body weight gains were recorded for males and females at 25000 mg/kg food (56% and 47% compared to controls for males and females, respectively). Dose-related inhibition of ChE activity in plasma (55-79%) and erythrocytes (54-90%) was noted for all doses in both sexes after 2 and 4 weeks. Dose-related inhibition of ChE activity in brain was noted after 4 weeks among males at 10000, 25000 and 50000 mg/kg food (12%, 14%, and 19%, respectively). Increased relative brain, kidneys and lung weights and decreased absolute spleen and heart weights were noted among males at 50000 mg/kg food. These changes in organ weight were attributed to differences in terminal body weights. Decreased absolute and relative (to body and brain) weights of the spleen were noted among females at 50000 mg/kg food. The significance of this finding is not clear, since no histopathology was performed.

In a 28 days study to investigate cholinesterase inhibition, doses of 0, 250 and 750 mg/kg food, equivalent to 0, 6 and 14 mg ethephon base 250/kg bw/day (corresponding to 0, 4.3 and 10 mg ethephon/kg bw/day) were tested in female dogs (not according to OECD). Acetone was used as vehicle. Erythrocyte acetylcholinesterase activity was depressed after a dose of 14 mg/kg bw/d (only from day 21 and further), as well as plasma cholinesterase activity from a dose of 6 mg/kg bw/d upwards, in a dose related fashion (from day 14 at 6 mg/kg bw and from day 7 at 14 mg/kg bw). No effects were observed on brain acetylcholinesterase activity.

A 1 year oral study was performed in dogs in accordance with OECD 409. Dose levels of 0, 100, 300, 1000 and 2000 mg/kg food, equivalent to 0, 2.79, 8.11, 27.37 and 54.17 mg/kg bw/day in males and 0, 2.55, 8.38, 29.71 and 49.96 mg/kg bw/day in females were used. Acetone was used as vehicle. No ChE measurements in plasma, erythrocytes and brain were performed. Therefore, the study can only be considered as supportive study. No effects on mortality, food and water consumption, haematology, clinical biochemistry and urinalysis were noted in a 1-year dietary toxicity study with dogs. A decrease in total body weight gain was noted in males and females of the 2000 mg/kg food dose group (the mean weight gain deficit relative to controls was 0.4 kg and 0.5 kg in males and females at 2000 ppm, respectively). A decrease in absolute spleen weight was noted among males given 2000 mg/kg food (55% when compared to control values). A decrease in relative spleen weight was noted in both males and females given 2000 mg/kg food (69 and 75% when compared to control values, respectively). A microscopic correlate for the spleen weight changes was not detected. A decrease in absolute thyroid weight (66% when compared to control values) and in absolute heart weight was noted in males given 2000 mg/kg food; these changes can be attributed to lower terminal body weights. At necropsy, macroscopic changes did not distinguish treated animals from controls. There were no treatment-related histopathological findings. No NOAEL could be established based the absence of data on ChE inhibition.

A 2 year dietary combined toxicity/carcinogenicity study was performed in rats in accordance with OECD 453. Dose levels of 0, 300, 3000, 10000 and 30000 mg/kg food, equivalent to 0, 13, 131, 446 and 1416 mg/kg bw/day in males and 0, 16, 161, 543 and 1794 mg/kg bw/day in females were used. Treatment did not affect the survival. An increased incidence of loose (semi-solid) faeces was observed in males at 30000 mg/kg food. An increased incidence of red and thickened ears was observed in females at 3000 ppm or higher, with a dose-related trend. Significantly lower body weights were recorded for males and females at 30000 ppm

throughout treatment; the weight gain deficits at the end of the first year of the study (relative to untreated controls) were 17% and 27% for males and females at 30000 ppm, respectively. Food consumption was significantly reduced in males and females at 30000 mg/kg food in the majority of measurement periods in the first year of treatment. Dose-dependent inhibition of plasma and erythrocyte ChE activities was noted at all dose levels: in plasma from males, the inhibition ranged from 17-44, 27-47, 38-67 and 45-56% at 300, 3000, 10000 and 30000 ppm, respectively, and in plasma from females from 15-27, 37-59, 47-65 and 56-72% at 300, 3000, 10000 and 30000 ppm, respectively; in erythrocytes from males, the inhibition ranged from 4-10, 39-47, 65-81 and 83-87% at 300, 3000, 10000 and 30000 ppm, respectively, and in erythrocytes from females from 9-19, 43-63, 72-79, and 82-86% at 300, 3000, 10000 and 30000 ppm, respectively. The observed inhibition of brain ChE activity (< 9%) was not considered biologically significant. Serum glucose was significantly lower for males and females at 30000 ppm after 26 weeks, and for males at 30000 ppm after 52 weeks. Serum phosphorus was significantly reduced for males at 30000 ppm after 13 and 26 weeks. There were slight perturbations in red blood cell parameters for males at 30000 ppm at several time points: erythrocyte counts were higher after 13 and 26 weeks, haematocrit was higher after 13 weeks, and MCHC was lower after 13, 26, 51 and 78 weeks. Prothrombin time was lower for females at 30000 ppm after 51 and 104 weeks. Urinary pH was significantly lower throughout the study for males and females at 10000 and 30000 ppm, with a dose-related trend. A significantly lower urinary pH was also recorded for females at 300 ppm after 103 weeks and for females at 3000 ppm after 77 and 103 weeks. Under control conditions for 4 weeks following 52-week exposure, the urinary pH returned to normal levels for males and females at 10000 and 30000 ppm. This effect is likely to be related to the acidity of the test substance. The specific gravity of urine was significantly higher for females at 10000 ppm and 30000 ppm after 50 and 77 weeks. In the investigations during week 77 females at 10000 and 30000 mg/kg food showed a strong decrease of urinary volume. Since this effect was incidental no relationship with treatment was suspected. At interim sacrifice after 52 weeks relative kidney weights were significantly higher for males and females at 30000 ppm. At terminal sacrifice, relative kidney weights were significantly higher for males at 3000 and 10000 ppm, and for males and females at 30000 ppm. All other deviations in absolute or relative organ weights at 10000 or 30000 ppm at interim and terminal sacrifice reflected lower terminal body weights. In the kidneys, the incidence of glomerulosclerosis was significantly increased in females at 30000 mg/kg food at terminal sacrifice. In the liver, the incidence of biliary hyperplasia was significantly higher in males at 30000 mg/kg food at terminal sacrifice.

A 1.5 year dietary carcinogenicity study was performed in mice in accordance with OECD 451. Dose levels of 0, 100, 1000, 10000 and 50000 mg/kg food, equivalent to 0, 14, 139 and 1477 mg/kg bw/day in males and 0, 17, 173 and 1782 mg/kg bw/day in females were used. In the 50,000 mg/kg food dose group animals showed severe morbidity or began to die after 2 days of treatment. Therefore this group was terminated and the study proceeded with the four remaining groups. After 52 and 70 days, 10/sex/dose were used for haematology and urine analysis and another 10/sex/dose for clinical chemistry and cholinesterase determinations. Females at 10000 ppm showed significantly lower body weights in weeks 61, 63, 67, and 75 and body weight gains were significantly lower in weeks 39, 47, 55, 57, 59, 61, 63, 67, 69, 71, and 75. The urinary pH was significantly lower in males at 1000 and 10000 ppm after 77 weeks, which was attributed to the acidity of the test substance. Urinary volume did not change significantly. Ethephon was determined to be a potent inhibitor of plasma ChE activity with dose-related inhibition (35-41 and 65-71% in the 1000 and 10000 ppm male dose groups, respectively, and 18-24, 41-61, and 74-76% in the 100, 1000, and 10000 ppm female dose groups, respectively). Similar results were observed in erythrocyte ChE activity measurements (35-36 and 70-72% in the 1000 and 10000 ppm male dose groups, respectively, and 21-36 and 60-74% in the 1000 and 10000 ppm female dose groups, respectively). Brain ChE activity was inhibited by 18% in females at 10000 ppm after 52 weeks.

5.6.2 Repeated dose toxicity: inhalation

No data available.

5.6.3 Repeated dose toxicity: dermal

A summary of repeated dose dermal toxicity data is presented in Table 5.6.3-1.

Table 5.6.3-1: Summary of repeated dose dermal toxicity data

Route/Test material	Duration Method/ Guideline	Species/ strain/ sex/ no. per group	Dose levels/ frequency of dosing	Effects	LOAEL (mg/kg bw/d)	NOAEL (mg/kg bw/d)
Dermal, occlusive Ethephon Technical-Base 250, sample no. 90400604 Purity 72.2%,	3 weeks OECD 410	Rabbit, Hra:NZW 10/sex/ dose	0, 25, 75 and 150 mg/kg bw/day, corresponding to 0, 18, 54 and 108 mg/kg bw/day, when corrected for purity 5 days/week, 6 hours/day	At all doses: macroscopic signs of dermal irritation (erythema, edema, desquamation and fissuring, all dose-related). At 150 mg/kg bw: histopathological changes in the treated skin areas (acanthosis in 1 male and 2 females and inflammation in 1 male and 3 females)	25 mg/kg bw/day, corresponding to 18 mg/kg bw day, when corrected for purity	-

Critical effects are presented in bold

A dermal study was performed in rabbits in accordance with OECD 410. No ChE measurements in plasma, erythrocytes and brain were performed. Histopathological examinations were limited to kidneys, liver, testes and skin. No treatment-related effects on mortality, clinical observations, haematology, clinical biochemistry, organ weights and histopathology (kidneys, liver) were noted. There were macroscopic signs of dermal irritation at all doses (erythema, edema, desquamation and fissuring), with a dose-related trend in incidence and severity. Histopathological changes in the treated skin areas were noted at 150 mg ethephon base 250/kg bw/day: acanthosis in 1 male and 2 females and inflammation in 1 male and 3 females. No histopathological investigations of treated skin areas were performed for the 75 and 25 mg/kg bw/day dose groups. Since no histopathological examination of the skin was performed at 25 and 75 mg/kg bw/day, the NOAEL for local effects was set at < 25 mg Ethephon Technical-Base 250/kg bw/day, which corresponds to <18 mg ethephon/kg bw/day. Since no ChE measurements were performed and histopathological examinations of treated skin areas were limited to kidneys, liver, testes and skin and confined to control and high dose animals in spite of signs of dermal irritation at all dose levels, the study is of limited value for the establishment of a NOAEL for systemic effects.

5.6.4 Other relevant information

5.6.5 Summary and discussion of repeated dose toxicity:

The main effect of repeated exposure to ethephon is inhibition of cholinesterase. Plasma cholinesterase inhibition is not considered to be toxicologically relevant, and therefore not relevant for classification. When the JMPR '98 criteria for cholinesterase inhibition are followed, where possible, limit values should be based on inhibition of brain cholinesterase instead of erythrocyte cholinesterase. Brain cholinesterase was inhibited at doses ≥ 50 mg/kg bw/day in a 14 day study in dogs. Cholinergic effects were also seen in rats in the acute neurotoxicity study at dose levels below the cholinergic effects in repeated dose studies in the rat. This indicates that these type of effects are acute effects and not repeated dose effects in the rat. It is assumed that this also applies to the dog. Therefore, no classification for repeated dose toxicity is proposed based on this study. Inhibition of brain cholinesterase was also observed at doses ≥ 4673 mg/kg bw/day in a 28 day study in rats and doses ≥ 1815 mg/kg bw/day in a 28 day study in mice. In a 78 week study in mice, brain ChE activity was reduced (18%) at 139 mg/kg bw/day. However, because the effect levels in the longer studies are above the guidance values for classification, classification is not considered necessary based on this endpoint.

In addition, body weight was significantly reduced (>20%) at doses ≥ 4673 mg/kg bw/day in a 28 day study in rats, as were absolute weights of heart, lung and brain. In the same study, spleen weight was reduced significantly at doses of 2299 mg/kg bw. In mice, bw was significantly reduced at doses of 4780 mg/kg bw/day and absolute spleen weight was decreased significantly at 10212 mg/kg bw/day (28 day study). In the 1 year study in dogs, body weight, absolute spleen weight and absolute thyroid weight were decreased at 49.96 mg/kg bw/day. In 2 combined toxicity/carcinogenicity study (2 years, rat), body weight and food intake were reduced at 1416 mg/kg bw. In addition, effects on blood glucose, serum phosphorus, red blood cell parameters and effects on kidney (weight and glomerulosclerosis) were observed only at doses ≥ 446 mg/kg bw/day. Also for these endpoints, the effect levels are above the guidance values for classification.

After repeated dermal administration, observed effects were related to irritation (erythema, edema, desquamation and fissuring). Since these effects are acute effects and since ethephon is already classified for irritation, no additional classification is necessary for repeated dermal exposure.

5.7 Mutagenicity (additional information)

5.7.1 *In vitro* data

An Ames test was performed with ethephon base 250 (purity: 72.3%) in accordance with OECD 471 of 1983, but not in accordance with the more recent OECD 471 guideline of 1997, since the Escherichia coli strain WP2uvra was not included. Sterile deionised water was used as vehicle and negative and positive controls included.

Toxicity was observed at 50 µl/plate in the strains TA1537, TA1538 and TA98. Ethephon base 250 induced point mutations in S. typhimurium in the absence and presence of metabolic activation in tester strain TA 1535 (dose related). Ethephon base 250 did not induce point mutations in S. typhimurium in the absence and presence of metabolic activation in tester strain TA 98, TA 100, TA 1537 and TA 1538.

Table 5.7.1-1: Results Ames test

Indicator cells	Endpoint	Results		Activation		Dose range
		- met act	+ met act	Tissue	Inducer	

Indicator cells	Endpoint	Results		Activation		Dose range
		- met act	+ met act	Tissue	Inducer	
B: *S. typh.* TA 98 TA 100 TA 1535 TA 1537 TA 1538	. point mut. point mut. point mut. point mut. point mut .	 - - + - -	 - - + - -	rat liver	Arochlor 1254	0.1, 0.5, 1, 2.5, 5, 10, 25 and 50 µl/plate

A gene mutation assay (HGPRT) was performed with ethephon base 250 (purity: 72.3%) in accordance with OECD 476 of 1984. The study does not fulfil the requirements of the more recent OECD 476 guideline of 1997, such as cytotoxicity criteria and number of dose levels tested. Culture medium with 5% FCS was used as vehicle and negative and positive controls included.

Cytotoxicity below 50% was only observed in the first experiment without metabolic activation and in the second experiment with metabolic activation. Ethephon base 250 did not induce gene mutations in CHO Chinese hamster ovary cells.

Table 5.7.1-2: Results gene mutation assay (HGPRT)

Indicator cells	Endpoint	Results		Activation		Dose range
		- met act	+ met act	Tissue	Inducer	
CHO Chinese hamster ovary cells	gene mutations (HGPRT)	-	-	rat liver	Arochlor 1254	Without metabolic activation: first exp.: 0.5, 1, 2 and 2.5 mg/ml Second exp.: 0.5, 1, 2, 2.2 and 2.4 mg/ml With metabolic activation: First exp.: 0.5, 1, 2 and 2.5 mg/ml Second experiment: 0.5, 1, 2, 2.2, 2.4 and 2.6 mg/ml

A chromosome aberration test was performed with ethephon base 250 in accordance with OECD 473 of 1983. The study does not fulfill the requirements of the more recent OECD 473 guideline of 1997, since no repeat experiment is performed. Cytotoxicity was observed at 1990 µg/ml (-S9). The confluence of the cultured CHO cells was 25% (% solvent control). In the presence of S9-mix the confluence of the cells was 88% at this concentration. Higher concentrations were not tested since the pH of the cultures was too low and this is incompatible with tissue culture. (pH at concentration of 2020 µg/ml was 6.5). Precipitation was not observed at any of the dose levels.

Ethephon base 250 did not induce chromosome aberrations in Chinese hamster ovary (CHO) cells.

Table 5.7.1-3: Results chromosome aberration assay

Indicator cells	Endpoint	Results		Activation		Dose range
		- met act	+ met act	Tissue	Inducer	
Chinese hamster ovary (CHO) cells	chromosome aberration	-	-	rat liver	Arochlor 1254	753, 1000, 1510 and 2010 µg/ml (-S9); 502, 1000, 1510 and 2010 µg/ml (+S9)

In addition, an unscheduled DNA synthesis assay was performed with ethephon base 250. However, the study was considered not acceptable since no appropriate toxicity was observed and in the second experiment only two dose levels were tested. Nevertheless, under the conditions of the study, ethephon base 250 did not induce UDS in hepatocytes treated in vitro and ethephon had no genotoxic activity in this test system.

5.7.2 *In vivo* data

Ethephon (technical base 250, purity 71.14%, batch C1045) was administered to rats at 800 and 2000 mg/kg bw (route not specified) in an unscheduled DNA synthesis assay according to OECD guideline 486. Exposure in the first experiment was 12-14 hours and in the second experiment 2-4 hours. Negative and positive controls (not further specified) were included.

Ethephon base 250 did not induce UDS in hepatocytes isolated ex vivo and ethephon had no genotoxic activity in this test system.

Table 5.7.2-1: Results in vivo unscheduled DNA synthesis assay

Endpoint	Species	Animal number	Results	Dose range
UDS (hepatocytes)	Rat	50 males/dose	-	800 and 2000 mg/kg bw

5.7.3 Human data

No data available.

5.7.4 Other relevant information

No data available.

5.7.5 Summary and discussion of mutagenicity

Although ethephon base 250 induced point mutations in S. typhimurium in the absence and presence of metabolic activation in tester strain TA 1535, in 4 other strains, Ethephon was negative. Ethephon Base 250 was also negative in a gene mutation test with CHO Chinese hamster ovary cells, an UDS test with rat hepatocytes (although the study was considered not acceptable) and a chromosome aberration test with CHO Chinese hamster ovary cells. Furthermore, ethephon base 250 was negative in an in vivo UDS test in rats. Therefore, ethephon base 250 is considered to be non-genotoxic and classification is considered not necessary.

5.8 Carcinogenicity (additional information)

5.8.1 Carcinogenicity: oral

A combined toxicity/carcinogenicity study was performed in Sprague Dawley CD® rats in accordance with OECD 453. For the evaluation of the carcinogenic potential of the test substance 90-100 animals/sex/dose were used. Doses of 0, 300, 3000, 10000 and 30000 mg/kg food were used (equal to 0, 13, 131, 446 and 1416 mg ethephon/kg bw/day in males and 0, 16, 161, 543 and 1794 mg/kg bw/day in females). Final sacrifices were in week 97 for males and in week 104 for females. In the liver, the incidence of biliary hyperplasia was significantly higher in males at 30000 mg/kg food at terminal sacrifice. Carcinogenicity was not demonstrated.

In addition, a 78-week carcinogenicity study in mice was performed in accordance with OECD 451. For the evaluation of the carcinogenic potential of the test substance 70 animals/sex/dose were used. 0, 100, 1000, 10000 and 50000 mg/kg food were used (equal to mean intake of 14, 139 and 1477 mg/kg bw/day for males and 17, 173 and 1782 mg ethephon/kg bw/day for females). Two tumour types in males (hepatocellular adenoma and lung adenoma) and two types in females (thymic region lymphosarcoma and lung adenoma) were observed in frequencies above 5%, but only the increased incidence of lung adenomas in males at 1000 mg/kg food reached the level of statistical significance. Since lung adenomas commonly occur in this strain of mouse and no dose-response was observed, this deviation was not considered to be related to treatment. No oncogenic potential of the test substance in mice was observed.

Table 5.8.1-1: Summary of neoplastic lesions in the 78 week study in mice.

Dose (ppm)	0		100		1000		10000	
	m	f	m	f	m	f	m	f
Liver: hepatocellular adenoma	6/69	1/70	10/69	0/69	4/70	0/69	8/70	0/69
Lung: adenoma	2/69	7/70	5/70	4/69	14/70	7/69	6/70	7/70
Thymus: lymphosarcoma	1/67	1/68	0/27	2/19	2/25	3/16	3/70	5/68

5.8.2 Carcinogenicity: inhalation

No data available.

5.8.3 Carcinogenicity: dermal

No data available.

5.8.4 Carcinogenicity: human data

No data available.

5.8.5 Other relevant information

No data available.

5.8.6 Summary and discussion of carcinogenicity

There was no evidence of treatment-related oncogenicity in the long-term oral mouse and rat studies. No oncogenic effects were observed up to 1477 mg/kg bw/day in mice and 1416 mg/kg bw/day in rats, the highest doses tested. No data were available regarding carcinogenic effects after dermal or inhalation exposure. In addition, no human carcinogenicity data were available. Based on the oral studies it is concluded that Ethephon does not need to be classified for carcinogenicity.

5.9 Toxicity for reproduction (additional information)

5.9.1 Effects on fertility

A 2-generation reproduction study was performed according to OECD 416. Sprague-Dawley Crl:CD®(SD)BR rats received 0, 300, 3000 and 30000 mg/kg food (equal to 0, 23, 231 and 2444 mg/kg bw/day (mean values for F0, F1A and F1B)). F0 females are mated twice to produce a F1A and F1B generation. Pups from the F1B generation were used to produce the F2A and F2B generations.

No treatment-related effects were observed on mating, fertility and gestation in F0 and F1 rats. In addition, no treatment-related effects were observed in reproductive organs. The NOAEL for reproduction toxicity is set at ≥ 30000 mg/kg food (equal to ≥ 2444 mg/kg bw/day). Results relevant for development are summarized under 5.9.2.

5.9.2 Developmental toxicity

A 2-generation reproduction study was performed according to OECD 416. Sprague-Dawley Crl:CD®(SD)BR rats received 0, 300, 3000 and 30000 mg/kg food (equal to 0, 23, 231 and 2444 mg/kg bw/day (mean values for F0, F1A and F1B)). F0 females are mated twice to produce a F1A and F1B generation. Pups from the F1B generation were used to produce the F2A and F2B generations. Results are summarized in table 5.9.2-1

Table 5.9.2-1: Results two-generation study of reproductive toxicity

Dose (mg/kg bw/day)	**0**		**23**		**231**		**2444**		**dr**
	m	**f**	**m**	**f**	**m**	**f**	**m**	**f**	
F0 animals									
Mortality	0/28	0/28	1/28	0/28	2/28	0/28	1/28	0/28	
Clinical signs									
-unkempt appearance							+		
-urinary stains							+		
-loose faeces							+	+	
Body weight							dc	dc	
Body weight gain							dc	dc	
Food consumption							d(c)	dc	
Mating/fertility/gestation	No treatment-related findings								
Oestrus cycle/mating index	No treatment-related findings								
Fertility/fecundity	No treatment-related findings								
Organ weight	No treatment-related findings								
Pathology									
macroscopy	No treatment-related findings								

Dose (mg/kg bw/day)	**0**		**23**		**231**		**2444**		**dr**
	m	**f**	**m**	**f**	**m**	**f**	**m**	**f**	
microscopy	No treatment-related findings								
F1 pups									
Litter size	No treatment-related findings								
Survival index									
- F1B live birth index							d		
- F1B 4-day survival index							d		
- F1B 7-day survival index					d				
Sex ratio	No treatment-related findings								
Body weight									
- F1A							dc	dc	
- F1B							dc	dc	
Pathology									
macroscopy	No treatment-related findings								
F1 animals									
Mortality									
- F1A	0/28	0/28	0/28	0/28	0/28	0/28	0/28	0/28	
- F1B	0/28	0/28	0/28	0/28	0/28	0/28	1/28	0/28	
Clinical signs (n=28)	7	0	4	1	10	4	28	28	
- loose faeces F1A									
- loose faeces F1B	9	4	13	6	18	7	26	28	
Body weight				d(c)	d(c)	d(c)	dc	dc	
Body weight gain							d(c)	d(c)	
Organ weight	No treatment-related findings								
Food consumption						d	dc	dc	
Mating/fertility/gestation	No treatment-related findings								
Pathology									
macroscopy	No treatment-related findings								
microscopy	No treatment-related findings								
F2 pups									
Litter size	No treatment-related findings								
Survival index									
- F2B live birth index							d		
- F2B 4-day survival index				d			d		
Sex ratio	No treatment-related findings								
Body weight									
F2A							dc	dc	
F2B					d(c)	d(c)	dc	dc	
Pathology									
macroscopy	No treatment-related findings								

dr dose related
dc/ic statistically significantly decreased/increased compared to the controls
d/i decreased/increased, but not statistically significantly compared to the controls
d(c) statistically significantly decreased during parts of the study period, while during other parts of the study the parameter was decreased but not statistically significantly.
a/r absolute/relative organ weight

Five parental males died during the study: 4 in the F0-generation and 1 in the F1. No relationship with treatment was established. During the 10-week pre-breed exposure, F0 males and females at 30000 mg/kg food (~ 2444 mg/kg bw) exhibited a reduction of body weight (gain) and food consumption, and an increased incidence of loose faeces. Females at 3000 mg/kg food (~ 231 mg/kg bw) showed reduced food consumption during the 3rd week of exposure, and an increased food consumption during the 1st and 6th week of exposure, hence this was not considered an adverse effect.

Significant reductions in gestational and lactational body weights were observed at 30000 mg/kg food. The F1A litters exhibited reduced body weights per litter at 30000 mg/kg food. During the second breeding of the F0 animals to produce F1B litters, gestational and lactational body weights were reduced at 30000 mg/kg food. An increased number of F1B stillborn pups

was observed at 30000 mg/kg food. F1B pup death was increased on postnatal days 0-4 at 30000 mg/kg food and on postnatal days 4-7 at 3000 mg/kg food, however, survival indices did not show any statistical difference. F1B pup body weights per litter were reduced at 30000 mg/kg food.

There were no treatment-related lesions observed in the necropsy of F1A and F1B pups which died during lactation, of randomly selected F1A and F1B pups or of F0 adults. There were also no treatment-related lesions observed in the histopathologic examination of selected organs from high dose and control F0 adults. While terminal body weights were reduced in F0 males and females at 30000 mg/kg food, absolute organ weights were unaffected by treatment. Effects on relative organ weights were considered secondary effects to reduced body weights.

During the 10-week exposure of the F1A animals, males at 30000 mg/kg food exhibited reductions in body weight (gain) and food consumption. At 3000 mg/kg food, F1A males showed only a slightly (<10%) reduced body weight (gain), mainly due to a lower initial body weight than controls and slightly decreased gain in week 0-2. F1A females at 30000 mg/kg food exhibited significantly reduced body weight throughout the 10-week exposure, and significantly reduced body weight gain 30000 mg/kg food. F1A females at 300 and 3000 mg/kg food showed a slight (<6%) but not dose-related body weight decrease only in week 0-6. Both males and females at 30000 mg/kg food exhibited increased incidences of loose faeces.

During the 10-week pre-breed exposure of F1B animals, reduced body weight (gain) and food consumption as well as increased incidences of loose faeces were observed at 30000 mg/kg food. Body weight gain was only slightly reduced in F1B males (week 2-3, and 9-10) at 3000 mg/kg food as well. In F1B males, a slightly increased incidence of loose faeces was observed at 3000 mg/kg food.

At the F1B breeding to produce F2A litters, maternal gestational and lactational body weight was reduced at 30000 mg/kg food. F2A pup body weights per litter were reduced at 30000 mg/kg food. Perinatal deaths and lactational survival were unaffected by treatment. During the second breeding of the F1B animals to produce F2B litters, maternal F1B gestational and lactational body weights were reduced at 30000 mg/kg food. The number of stillborn F2B pups and perinatal deaths were increased at 30000 mg/kg food. F2B pup body weights per litter were reduced at 30000 mg/kg food. At 3000 mg/kg food, body weights per litter were only slightly reduced (<7%) on days 21 and day 28 only.

There were no treatment-related lesions observed in the necropsy of F2A and F2B pups which died during lactation, of randomly selected F2A and F2B pups, or of F1B adults. There were also no treatment-related lesions observed in the histopathologic examination of selected organs from high dose and control F1B adults. Terminal body weights were reduced in F1B males and females at 30000 mg/kg food. Effects on relative organ weights were considered secondary effects to reduced body weights.

Based on significant effects on body weight and food consumption at 30000 mg/kg food, the NOAEL for maternal toxicity is 3000 mg/kg food (equal to 231 mg/kg bw/day in males and females). Based on reduced F1 and F2 litter weight, and increased still births and deaths during early lactation in F1B and F2B litters at 30000 mg/kg food the NOAEL for developmental toxicity is also set at 3000 mg/kg food. The acceptability of the study is questionable, because no ChE measurements in plasma, erythrocytes and brain were performed. Thus, the NOAEL for ChE inhibition remains a matter of conjecture.

A teratogenicity study with rats was performed in accordance with OECD 414, although this guideline was not mentioned in the report. Rats were dosed by gavage (10 ml/kg bw) with doses of 0, 125, 250 or 500 mg ethephon technical – base 250/kg bw (purity 71.7%), on gestational days 6-15. Dose levels were adjusted for purity of test substance. Distilled water was used as vehicle. Mating procedures involved one male and one female. Results are summarized in table 5.9.2-2

Table 5.9.2-2: Results developmental study in rats

Dose (mg/kg bw/day)	**0**	**125**	**250**	**500**	**dr**
Maternal effects					
Mortality	None				
Clinical signs	No treatment-related findings				
Pregnant animals	23	21	22	22	
Body weight (gain)	No treatment-related findings				
Uterus/dam weight ratio	No treatment-related findings				
Food consumption	No data				
Pathology					
Macroscopy					
– Mottled kidney	1	1	1	2	
– Circumscribed area adhered to the diaphragm	0	0	0	1	
Litter response					
Live foetuses	No treatment-related findings				
Foetal weight	No treatment-related findings				
Post implantation loss	No treatment-related findings				
Sex ratio	No treatment-related findings				
Examination of the foetuses					
External observations					
– Short thickened body	0/337	0/316	1/350	0/331	
Skeletal findings					
Incomplete/absent ossification	No treatment related findings				
Visceral findings	No treatment related findings				

dr dose related
dc/ic statistically significantly decreased/increased compared to the controls
d/i decreased/increased, but not statistically significantly compared to the controls
a/r absolute/relative organ weight

No treatment-related signs of toxicity were noted in the dams. Survival rates were 100% at all dose levels. There were no treatment-related clinical signs or parental necropsy observations. Between day 12 and 16 of gestation body weight gain was significantly increased in dams treated at 250 and 500 mg/kg bw/day (18% and 17% of control values, respectively). This deviation is considered of no toxicological relevance.

There were no significant differences in the number of corpora lutea or implantations, implantation efficiency, the number or percentage of live or resorbed foetuses, or mean foetal weights. Examination of the foetuses revealed no significant deviations in the incidence of external, soft tissue, or skeletal anomalies.

Based on the absence of effects in maternal females, the NOAEL for maternal toxicity was set at ≥ 500 mg/kg bw/day. No developmental effects were observed at any of the doses tested. Therefore the NOAEL for developmental toxicity was set at ≥ 500 mg/kg bw/day. Since no teratogenic effects were reported, the NOAEL for teratogenic effects was set at ≥ 500 mg/kg bw/day. The acceptability of the study is questionable, because no ChE measurements in plasma, erythrocytes and brain were performed. Thus, the NOAEL for ChE inhibition remains a matter of conjecture.

In addition, a developmental study was performed in rabbits in accordance with OECD 414, although this guideline was not mentioned in the report. Rabbits were dosed by gavage (2 ml/kg bw) with doses of 0, 62.5, 125 or 250 mg ethephon technical –base 250/kg bw (purity 72.2%), on gestational days 7-19. Dose levels were adjusted for purity of test substance. Deionised water was used as vehicle. The females were artificially inseminated. Results are summarized in table 5.9.2-3

Table 5.9.2-3: Results developmental study in rabbits

Dose (mg/kg bw/day)	**0**	**62.5**	**125**	**250**	**dr**
Maternal effects					
Mortality	1/22	2/22	1/22	19/22	
Clinical signs					
Ataxia/reduced activity/prostrate				+ +	
Yellow stained anogenital area					
Pregnant animals	21	21	20	18	
Pregnant at Caesarean section	21	19	19	2	
Body weight (gain)			(dc)	dc	
Uterus/dam weight ratio	No treatment-related findings				
Food consumption	No data				
Pathology					
Macroscopy (no. of animals)	2	0	0	8	
– Stomach: erosion/reddened/with black foci	0	2	1	15	
– Uterus with normally developing implants at time of sacrifice					
Litter response					
Live foetuses				d	
Foetal weight	No treatment-related findings				
Resorptions [mean/dam]	0.5	0.4	0.7	2.0	
- early	0.4	0.1	0.3	0.0	
- late					
Post implantation loss [%]	12	5	16	43	
Sex ratio	No treatment-related findings				
Examination of the foetuses					
External observations	No treatment related findings				
Skeletal findings	No treatment related findings				
Visceral findings	No treatment related findings				

dr dose related
dc/ic statistically significantly decreased/increased compared to the controls
d/i decreased/increased, but not statistically significantly compared to the controls
a/r absolute/relative organ weight

The deaths of 1 control doe, 2 does at 62.5 mg/kg bw, and one doe each at 125 mg/kg bw/day groups or 250 mg/kg bw/day were due to intubation errors, and not related to treatment with the test substance. Test material-related deaths occurred at 250 mg/kg bw; 3 does died and 14 does were sacrificed moribund. Additionally, 1 dam at 250 mg/kg bw was euthanised because of an eye lesion (buphthalmos and corneal opacity). Clinical signs of toxicity observed in 17 of 22 does in the high dose group included ataxia, reduced activity, prostration, and/or yellow stained anogenital area. Does at 250 mg/kg bw lost weight between day 7 and 16 of gestation. The 2 pregnant does at 250 mg/kg bw that survived had weight losses for days 16 to 20 of gestation. Body weights were significantly reduced at 250 mg/kg bw on day 13 (88% of control values). At 125 mg/kg bw significantly reduced body weight gain was observed between day 13 and 16 of gestation (50% compared to controls), but body weight gain over the whole study period was within control values. Macroscopic examination of

does revealed erosions, reddened area and black foci in the stomach at a greater incidence at 250 mg/kg bw/day (8 does) than in controls (2 does). The percent of early resorptions and post-implantation losses were considerably higher and the percent of live foetuses was lower in the 2 remaining dams at 250 mg/kg bw. This is reflected in the lowered number of foetuses per litter at this dose level. There were no test material-related foetal external, soft tissue, or skeletal variations or malformations.

Based on maternal death, depressions in body weights and body weight changes, treatment-related clinical signs and macroscopic findings at 250 mg/kg bw, the NOAEL for maternal and developmental toxicity was set at 125 mg/kg bw. Since no teratogenic effects were reported, the NOAEL for teratogenic effects was set at ≥ 250 mg/kg bw. The acceptability of the study is questionable, because no ChE measurements in plasma, erythrocytes and brain were performed. Thus, the NOAEL for ChE inhibition remains a matter of conjecture.

5.9.3 Human data

No data available.

5.9.4 Other relevant information

No data available.

5.9.5 Summary and discussion of reproductive toxicity

The results of reproduction toxicity and developmental studies are summarised in table 5.9.5-1.

Table 5.9.5-1 Summary of reproduction toxicity and developmental studies with ethephon

Species		NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical effects
2-Generation reproduction toxicity				
rat	parental	231	2444	Decreased body weight gains and food consumption Lower F1 and F2 pup weights, decreased survival of F1B and F2B pups
	developmental	231	2444	No effects.
	reproduction	≥ 2444	-	
Teratogenicity				
rat	maternal	≥ 500	-	No toxicologically relevant effects
	developmental	≥ 500	-	No toxicologically relevant effects
	teratogenicity	≥ 500	-	No toxicologically relevant effects.
rabbit	maternal	125	250	Mortality, weight loss, clinical signs and macroscopy.
	developmental	125	250	Death of dams, increased pre- and post implantation loss, reduced number of live foetuses and reduced foetal weight.
	teratogenicity	≥ 250	-	No effect.

In an oral 2-generation reproduction study in rats, the NOAEL for reproductive effects was ≥ 2444 mg/kg bw/day, since no effects on mating performance or fertility were noted. At 2444 mg/kg bw/day, parental effects included decreased body weight (gain) and decreased food consumption of F0 and F1 males and females. No treatment-related adverse effects were observed in adult animals at lower dose levels. Thus, classification for reproductive effects is not necessary.

In the oral 2-generation reproduction study in rats, developmental effects were only observed at 2444 mg/kg bw/d and included reduced litter weight in F1 and F2 pups, increased still births and deaths during early lactation in F1B and F2B litters. At the same dose, also maternal toxicity was observed, including reduced body weight and clinical signs of toxicity. Therefore, the effects observed in the pups are probably secondary to maternal toxicity. No treatment-related lesions were observed at necropsy.

In a developmental study in rats, no treatment-related clinical signs or parental necropsy observations were reported. In addition, no developmental or teratogenic effects were observed at doses up to 500 mg/kg bw. In a developmental study in rabbits, treatment related mortality was observed at 250 mg/kg bw/day as well as clinical signs of toxicity and weight loss in the does. Macroscopic examination of does revealed erosions, reddened area and black foci in the stomach at a greater incidence at 250 mg/kg bw/day than in controls. The percent of early resorptions and post-implantation losses were considerably higher and the percent of live foetuses was lower in the remaining dams at 250 mg/kg bw, reflected in a lowered number of foetuses per litter (i.e. only at doses that caused maternal toxicity). These effects are probably secondary to the maternal toxicity. Teratogenic effects were not observed.

Both in the 2 generation study and the teratogenicity studies, no ChE measurements in plasma, erythrocytes and brain were performed. Therefore, the NOAEL for parental toxicity in these studies is tentative. Nevertheless, based on the observed effects, classification for developmental effects is considered not necessary according to the criteria of DSD and CLP, since developmental effects were only observed at a dose that also induced maternal toxicity.

5.10 Other effects

5.11 Derivation of DNEL(s) or other quantitative or qualitative measure for dose response

Not relevant for this type of report.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES (additional information)

6.1 Explosivity

According to the results of the tests on explosive properties (EEC Method A14) with the technical active substance (purity 70.2%), ethephon is not explosive (Francois, 1999) (DAR B.2.1.22 (IIA 2.13)). Therefore, it can be concluded that ethephon has no explosive properties and does not require classification for explosivity.

6.2 Flammability

According to the results of the tests for flammability and auto-flammability (EEC Method A15) with the technical active substance (purity 70.2%), ethephon has a self ignition temperature of 490 °C (Francois, 1999) (DAR B.2.1.20 (IIA 2.11)). Therefore, classification for flammability is not required. EEC Method A10 was not applicable, since the test substance is a liquid

6.3 Oxidising potential

The ethephon molecule only contains a chloroethylphosphonic acid and does not contain substituens or radical which has oxidative properties, also technical ethephon is a solution of 71% ethephon in water (Bascou, 2003) (DAR B.2.1.23 (IIA 2.15)). Therefore, it can be concluded that ethephon has no oxidising properties and does not require classification.

7 ENVIRONMENTAL HAZARD ASSESSMENT

The proposal is a revision of the current entry in Annex VI to the CLP regulation (29th ATP, 2004). The environmental hazard assessment for ethephon is based on the Draft Assessment Report, the Addendum to the Draft Assessment Report and Proposed Decision of the Netherlands prepared in the context of the possible inclusion of ethephon in Annex I of Council Directive 91/414/EEC (DAR January 2006 + addendum June 2008, RMS The Netherlands) concerning placing ethephon on the market as a plant protection product (PPP).

Ethephon was also discussed in the TC-C&L in January 2007 (Summary record ECB/08/07) within the framework of Directive 67/548/EEC. The conclusion of this discussion was that ethephon needed not be classified for the environment. A summary of the discussion can be found in Annex 2.

The current classification proposal takes into account the criteria for classification for the aquatic environment which are included in the 2nd ATP to the CLP Regulation.

All tables in the present assessment are copied from the DAR or the addendum to the DAR. The tables are renumbered in accordance with the paragraph numbers.

7.1 Aquatic compartment (including sediment)

7.1.1 Toxicity test results

7.1.1.1 Fish

Short-term toxicity to fish

Study 1

The acute toxicity of ethephon technical concentrate (purity 72.1%) to rainbow trout (*Oncorhynchus mykiss*) was determined under semi-static conditions (daily renewal of test media) in a 96h test. The test was carried out in compliance with GLP (with exception of the chemical analysis) and according to the OECD 203 guideline. Groups of ten fish were exposed to nominal test concentrations of 100, 180, 320, 560 and 1000 mg ethephon/L. Measured concentrations were between 9.1% and 56.0% of the nominal concentrations; these poor recoveries qualify this study as less reliable.

The cumulative mortality after 96 hours is given in Table 7.1.1.1-1.

Table 7.1.1.1-1. Cumulative mortality percentage in the acute test with rainbow trout (*Oncorhynchus mykiss*).

Nominal test substance concentration (mg/L)	0	100	180	320	560	1000
Cumulative mortality after 96h (%)	0	0	0	0	10	100

All fish exposed to 1000 mg ethephon/L died within 3 hours; this effect is most likely caused by the low pH value of 2.7. Loss of equilibrium was observed at 180 and 320 mg/L during approximately 1 hour after the start of the test and by transfer of fish at each renewal of the test media. This can most likely be attributed to fluctuation in pH at replacement. The calculated nominal 96h-LC50 value was 720 mg ethephon/L (95% confidence limits 640 – 810). This corresponds with a LC50 of 519 mg (461 – 584) ethephon/L.

Based on measured concentrations, the worst-case LC50 is 47 mg ethephon/L.

Study 2

The acute toxicity of ethephon (purity 98%) to the carp (*Cyprinus carpio*) was investigated under continuous flow-through conditions in a 96h limit-test (one concentration of 100 mg/L), pH 7.9-8.4, in compliance with GLP and according to OECD 203 and EC C.1.

Measured ethephon concentrations were 97.0 - 118.5% of nominal. Observations for mortality and adverse effects after 3h, 6h, 24h, 48h 72h and 96h and showed no adverse effects with respect to these parameters at the only ethephon concentration of 100 mg/L or in the control; it is concluded that the 96h-LC50 is > 100 mg ethephon/L and the NOEC for mortality is 100 mg ethephon/L.

Long-term toxicity to fish

The toxicity of ethephon technical concentrate (purity 71.4%) to early life stages of the fathead minnow *Pimephales promelas*) was assessed in a 34-day study using an intermittent flow-through system with 6.6 times replacement in 24 hours. Effect parameters were hatching, larval survival and growth. Nominal concentrations tested were 5.1, 10, 20, 40 and 81 mg ethephon/L. The study was carried out in compliance with GLP and according to the OECD Guideline 210.

Measured concentrations were 94% of nominal on average. Based on the measured concentrations, the exposure levels were defined as 5, 10, 21, 43 and 89 mg ethephon/L. At completion of the hatching period (t = 4 days) the average control survival percentage was 73%. At the highest ethephon concentration all embryos died. At the other mean measured exposure concentrations, the survival of the embryos was not significantly different from the control.

At the end of the test (30 days post hatch), the survival, total length, mean wet/dry weight of the larvae at concentrations up to 43 mg ethephon/L was not significantly different from the control.

Based on the most sensitive parameter (embryo survival), the LOEC and NOEC of ethephon technical concentrate to the fathead minnow was determined to be 89 and 43 mg ethephon/L respectively.

7.1.1.2 Aquatic invertebrates

Short-term toxicity to aquatic invertebrates

The acute toxicity of ethephon technical concentrate (purity 72.1%) to Daphnia magna was determined under static conditions in a 48h test. Daphnids were exposed to nominal test concentrations of 64.2, 111.1, 192.5, 333.3, 577.4 and 1000 mg ethephon/L. The test was carried out in compliance with GLP and according to OECD 202 (Part I). Chemical analysis of the test media was not performed.

During the test, the temperature in the test media was 20°C, the oxygen concentration varied between 10.3 and 11.6 mg O2/L and the pH ranged between 7.8 and 8.6.

There was no immobility in the control; at 1000 mg/L one immobile daphnid (out of twenty) was found. Therefore, the 48h-EC50 is > 1000 mg/L.

The results of this study are based on nominal concentrations; in view of the fast hydrolysis rate reported this study may therefore underestimate the toxicity of ethephon to daphnia.

Long-term toxicity to aquatic invertebrates

The chronic toxicity of ethephon technical concentrate (71.2%) to *Daphnia magna* was assessed in a 21-day study under intermittent flow-through conditions. Nominal concentrations tested were 9.4, 19, 38, 75 and 150 mg ethephon/L. The study was carried out in compliance with GLP and according to the US EPA FIFRA Guideline no. 72-4.

Analyses of the test substance concentrations in the exposure media were carried out before the start of the test and weekly during the test, showing an average of 94% of the nominal concentrations. Based on the measured concentrations the exposure levels were defined as 8.5, 17, 38, 67 and 160 mg ethephon/L.

No significant changes in the survival of daphnids were observed at any of the concentrations tested. At the highest test substance concentration (160 mg ethephon/L) the mean cumulative number of offspring was 182; this is significantly less compared to the control. At lower exposure concentrations there were no significant effects with respect to reproduction.

At the highest test substance concentration, the mean the total body length and dry weight was significantly reduced when compared with the control animals. At the lower concentrations tested there were no significant effects.

Based on the adverse effects on reproduction and to growth, the LOEC and NOEC for ethephon technically was 160 mg ethephon/L and 67 mg ethephon/L, respectively. The LC50 was > 160 mg ethephon/L.

7.1.1.3 Algae and aquatic plants

Study 1 - Algae

The toxicity of ethephon technical concentrate (purity 72.1%) to the algae *Chlorella vulgaris* was determined in a 72h algal growth inhibition test. Nominal test concentrations were 5.0, 10, 20, 40 and 80 mg ethephon/L. The test was carried out in compliance with GLP and according to OECD 201.

The cultures were incubated under continuous illumination with a light intensity of approximately 7000 lux at a temperature of 24 ± 1°C. The pH was measured at t = 0h (pH ranged from 7.2-8.1) and 72h (ranged from 8.4-9.9). At t = 0, 24h, 48h and 72h the absorbance of all cultures was measured at 665 nm. The percentage inhibition, based on growth rate and biomass (area under the growth curve), was calculated.

No ethephon was detected in samples taken at test initiation and termination. For various cultures, the pH increase during the test exceeded the maximum of the guideline which is 1.5 log units. This might be due to the relatively high initial cell density. The nominal 24-48h ErC50 was calculated to be 32 mg/L and the nominal 72h-EbC50 was calculated to be 29 mg/L. The NOEC was 5 mg/L.

RMS has calculated the nominal 0-72h ErC50 according to a model for logistic growth, described by Kooyman et al. (1983)[1]. The result was a nominal 0-72h ErC50 of 33 mg/L. Based on ethephon content in the sample used for the study the 72h EbC50 and 72h ErC50 are respectively 20.9 and 23.8 mg ethephon/L.

The results of this study are based on nominal concentrations; in view of the fast hydrolysis rate reported this study may therefore underestimate the toxicity of ethephon to algae.

1)Kooyman, S.A.L.M., A.O. Hanstveit, H. Oldersma, *Parametric analysis of population growth in bioassays.*, Water Research 17, pp527-538 (1983)

Study 2 - Algae

The toxicity of ethephon technical concentrate (purity 71.9%) to the green algae *Pseudokirchneriella subcapitata* (formerly known as *Selenastrum capricornutum*) was determined in a 120h algal growth inhibition test. Only one concentration of 1.5 mg ethephon/L was tested. The test was carried out in compliance with GLP and according to EPA FIFRA § 122-2 and § 122-3.

The cultures were incubated under continuous illumination with a light intensity of 4000-5000 lux at a temperature of 24± 1°C. The pH was 7.4 in the controls and 6.9 in the Ethephon test solution at the start of the test. At the end of the test, the pH value had increased to 10.4.

Whereas measured concentrations of the test solution and the stock solution were 95% and 96 % of nominal at t = 0h, respectively, no detectable ethephon remained in the test solution and the stock solution after 120 hours. This was believed to be the result of alkaline hydrolysis, which is very likely to occur at high pH values as found in the test.

The mean cell densities in the flasks containing 1.5 mg ethephon/L (corresponding with a measured concentration at the start of the test of 1.4 mg ethephon/L) were not significantly different from the cell densities in the control flasks. It is therefore concluded (by RMS) that the 120h-EC50 > 1.4 mg ethephon/L and the NOEC ≥ 1.4 mg ethephon/L, based on the initial measured concentration.

Study 3 - Algae

The toxicity of ethephon technical concentrate (purity 71.9%) to the bluegreen algae Anabaena flos-aquae was determined in a 120h algal growth inhibition test. Only one concentration of 1.8 mg ethephon/L was tested. The test was carried out in compliance with GLP and according to EPA FIFRA § 122-2 and § 122-3.

The cultures were incubated under continuous illumination with a light intensity of 2000-3000 lux at a temperature of 23-24°C. The pH value ranged from 7.4-7.7.

Whereas the measured concentration of the test solution was 121% of nominal at t = 0h, no detectable ethephon remained in the test solution after 120 hours. This was believed to be the result of alkaline hydrolysis and considered as unavoidable under the static test conditions used.

The cell densities in the flasks exposed to an initial ethephon concentration of 1.8 mg ethephon/L were 97, 62, 87, 130 and 108% of the mean cell density of the controls at respectively 0, 24, 48, 72, 96 and 120h. It is therefore concluded (by RMS) that the 120h-EC50 is > 1.8 mg ethephon/L and the NOEC ≥ 1.8 mg ethephon/L, based on the measured concentration at test start.

Study 4 - Algae

The toxicity of ethephon technical concentrate (purity 71.9%) to the diatom *Navicula pelliculosa* was determined in a 120h growth inhibition test. Only one concentration of 1.5 mg ethephon/L was tested. The test was carried out in compliance with GLP and EPA FIFRA § 122-2 and § 122-3.

The cultures were incubated under continuous illumination with a light intensity of 4000-5000 lux at a temperature of 23-24 °C. The pH of the controls increased from 7.3 (t = 0h) to 7.5 (t = 120h). The pH of the test solution increased from 7.0 (t = 0h) to 9.1 (t = 120h).

Whereas the measured concentration of the test solution was 101% of nominal at t = 0h, it had decreased to 7.3% of nominal after 120 hours. This was believed to be the result of alkaline hydrolysis, which is considered by the authors as unavoidable.

The cell densities in the flasks containing 1.5 mg ethephon/L were respectively 213, 70, 134, 115 and 113% of the mean cell density of the controls. It is therefore concluded (by RMS) that the 120h-EC50 > 1.5 mg ethephon/L and the NOEC ≥ 1.5 mg ethephon/L, based on the nominal concentration.

The results of this study are based on nominal concentrations; in view of the fast hydrolysis rate reported this study may therefore underestimate the toxicity of ethephon to algae.

Study 5 - Aquatic plants

The toxicity of ethephon technical concentrate (purity 71.9%) to the fresh water plant *Lemna gibba* G3 (duckweed) was determined in a semi-static phytotoxicity test at a pH around 5. Nominal test concentrations were 0.090, 0.19, 0.39, 0.75 and 1.5 mg ethephon/L. The test was carried out in compliance with GLP and according to EPA FIFRA § 122-2 and § 122-3. The number of fronds was counted after 3, 6, 9, 12 and 14 days. The test was carried out in an environmental test chamber controlled with respect to temperature (25 ± 2°C) and light intensity.

The average concentrations for the four sets of analyses were between 90% and 115% of the nominal concentrations: mean measured concentrations were 0.10, 0.17, 0.44, 0.81 and 1.6 mg ethephon/L. The average number of fronds per replicate was 46% reduced at the highest concentration tested (1.5 mg ethephon/L). Based on these results, it is concluded that the 14d-EC50 is just above 1.5 mg ethephon/L (actual measured concentration 1.6 mg ethephon/L). Statistical significant effects were found at all concentrations; therefore the 14d-NOEC was < 0.10 mg ethephon/L. For this reason the 14d-EC10 of the average specific growth rate was calculated, based on the slope of the regression line in a plot of ln N versus time, considering that there was exponential growth in the control, no significant periods of lag or stagnancy was observed and the course of the growth curve was monotonous. The calculation resulted in a value of 0.21 mg ethephon/l

7.1.1.4 Sediment organisms

No data on the toxicity of ethephon for sediment dwelling species were submitted.

7.2 Conclusion on the environmental classification and labelling

Based on the available information on acute and chronic aquatic toxicity aquatic plants are most sensitive to ethephon. The lowest ErC50 and ErC10 values observed for *Lemna gibba* after 14 days is 1.6 mg ethephon/l (which is in the toxicity range of 1 mg/l ≤ 1 mg/l according to Annex VI to DSD) and 0.21 mg ethephon/l (which is > 0.1 to ≤ 1 mg/l according to Table 4.1.0(b)(i) of Annex I to CLP), respectively, based on growth rate and mean measured concentrations.

The log Kow of ethephon is -1.89 at neutral pH is lower than the criteria for bioaccumation in CLP (log Kow >4) and Directive 67/548/EEC (log Kow > 3). Ethephon therefore does not fulfil the criterion for bioaccumulation.

Based on the results from the ready biodegradation study, the hydrolysis study and the two simulation studies RAC concludes that ethephon does not undergo a fast primary degradation and cannot, therefore, be regarded as rapidly degradable. Taking into consideration the results of the acute aquatic toxicity studies (14d-EC50 = 1.6 mg a.s./l) it can be concluded that ethephon should be classified as dangerous to the aquatic environment with N; R51-53 according to the criteria of Directive 67/548/EEC.

Furthermore, based on the lack of rapid degradation and the lowest ErC10 for chronic aquatic toxicity for the aquatic plant *L. gibba* (0.21 mg ethephon/l), ethephon should be classified with

Aquatic Chronic 2 – H411 according to the revised criteria of the CLP Regulation included in the 2nd ATP to the CLP Regulation (March 2011).

Conclusion of environmental classification according to Directive 67/548/EEC

All acute EC50 values for ethephon are > 1 mg/L.

Ethephon is not considered rapidly degradable.

The log Kow value of ethephon is < 3.

Based on this information, it can be concluded that ethephon should be classified as dangerous to the aquatic environment with N; R51-53 according to the criteria of Directive 67/548/EEC.

Conclusion of environmental classification according to CLP (including the criteria of the 2nd ATP)

Aquatic acute toxicity:

All acute EC50 values for ethephon are > 1 mg/L.

Based on this information, ethephon does not fulfil the criteria for aquatic acute classification.

Aquatic chronic toxicity:

Chronic data are available for all trophic levels. The lowest value (i.e. EC10 value observed for aquatic plants) is ≥ 0.1 and <1.0 mg/l.

Ethephon is not considered rapidly degradable.

The log Kow value of ethephon is < 4.

Based on this information, ethephon should be classified with Aquatic Chronic 2 – H411 according to the revised criteria of the CLP Regulation included in the 2nd ATP to the CLP Regulation (March 2011).

JUSTIFICATION THAT ACTION IS REQUIRED ON A COMMUNITY-WIDE BASIS

Ethephon is an active substance in the meaning of Directive 91/414/EEC and therefore subject to harmonised classification and labelling (Regulation EC 1272/2008 article 36.2).

Ethephon was included in Annex I of Directive 67/548 in 2004 (29th ATP; Commission Directive 2004/73/EC of 29 April). A discussion regarding a change of the classification took place at the TC C&L in November 2006 (Summary record ECB/20/07, see Annex I). The TC C&L discussion was related to acute toxicity, skin sensitization and corrosivity. TC C&L agreed ethephon should be classified as Xn; R20/21/22 – C; R34. Based on the majority opinion of the TC C&L, ethephon does not need to be classified for sensitization. These TC C&L conclusion was, however, not included in Annex I of Directive EC 67/548 and consequently Annex VI of Regulation EC 1272/2008 still includes the previous C&L regarding human health.

A discussion regarding change of classification of ethephon for the environment took place at the TC C&L in January 2007 (Summary record ECB/08/07, see Annex II). Based on the rapid degradation of ethephon and the formation of non-classifiable metabolites, TC C&L decided not to classify ethephon as hazardous to the environment.

To implement the agreed modifications, this proposal to modify the harmonised classification and labelling is prepared.

OTHER INFORMATION

This proposal for harmonised classification and labelling is based on the data provided for the registration of the active substance ethephon according to Directive 91/414/EEC. The summaries included in this proposal are partly copied from the DAR. Some details of the summaries were not included when considered not relevant for a decision on the classification and labelling of this substance. For more details the reader is referred to the DAR.

REFERENCES

European Commission. Revised Draft Assessment Report Ethephon, prepared by The Netherlands, January 2006

European Commission. Revised Addendum Ethephon, prepared by The Netherlands, January 2006

European Commission. Revised ARfD Addendum Ethephon, prepared by The Netherlands, October 2006

European Commission. Addendum 2 on ARfD Ethephon, prepared by The Netherlands, June 2008

ANNEX 1

Conclusions of the discussion from the TC-C&L in November 2006 (Summary record ECB/20/07/Rev2) (exerpts only).

Ethephon P509 (NL)
(Index No: 015-154-00-4, CAS No: 16672-87-0, EC No: 240-718-3)

Current classification in Annex I: Xn; R20/21 - C; R34 - R52-53

Proposal: [Xn; R20/21/22 - C; R34][NC for environment] *(environment to be discussed in January 2007)*

ECBI/79/06: **Classification proposal from NL**

ECBI/79/06 Add. 3: **Classification proposal from NL**

NL said that the discussion could be concentrated to Xn; R22 and R43 which were the controversial end-points.

Acute Toxicity

TC C&L confirmed classification with Xn; R20/21 which also is the current classification in Annex I.

In addition **NL** proposed that the substance to be classified was the substance without solvent why it would be necessary to recalculate the data provided and remain with R22.

In the written procedure prior the meeting **BE** and **ES** did not support this proposal while **IRL** did support the NL conclusion.

EL asked about the marketed product and whether the substance was stable without the solvent.

IND informed that the pure ethephon was not marketed. They had also performed an acute neurotoxicity study and from this they had re-calculated the acute toxicity values and found that they were outside classification limits.

UK remarked that in the summary of the neurotoxicity study it was not completely clear what were the doses applied. They agreed with NL strategy in this case and said that it could be possible to set SCL based on the solvent data but it was the substance itself that must be listed in Annex I.

IND was asked to provide the neurotoxocity study to the TC C&L. IND promised to provide further detail in a position paper.

IRL agreed with NL that the classification must be made on the active itself and that R22 should be applied.

DK also agreed with R22 and the reasoning put forward by NL and other experts supporting the NL proposal.

ECB concluded that the TC C&L provisionally agreed to add that classification Xn; R22 for acute toxicity to the current Annex I entry. The detailed data would be made available by IND in the Follow-up period when a final decision could be made. Member States not writing in

their none approval would be assumed to support the provisional recommendation agreed at the meeting to classify with Xn; R22.

UK suggested Specific Concentration Limits for R22 at 70%. **NL** did not believe that this was necessary as data existed for the preparation on the market. **IND** supported the position of NL in this case and no Specific Concentration Limits were added for R22.

Skin sensitisation

UK, **BE** and **ES** did not agree to the NL proposal in the written procedure prior the meeting.

NL said that the number of animals was too low in one study. There was Guineapig Maximisation Tests (GMT) that showed positive results even if these were not the usual effects seen in this type of study. According to them it was an open discussion whether these effects in the GMT were regarded as positive or not.

UK did not think that the skin findings in the GMT could be interpreted as sensitisation reaction but rather due to the low pH of the substance. Therefore they did not support R43 classification in this case. In addition the other studies reported were negative.

BE, **DE**, **FR, N** and **EL** expressed their agreement to the interpretation made by UK.

DK had difficulties to understand how the effects seen could be related to something else than to sensitisation. They supported to classify based on these observations.

No classification for sensitisation was then agreed based on the majority opinion of the TC C&L.

Corrosivity

TC C&L confirmed the current Annex I classification with C; R34. NL suggested adding R37 in the Specific Concentration Limits in the interval 5-10%. This was agreed by the TC C&L.

Conclusion:

The TC C&L confirmed the current classification Xn; R20/21 – C; R34 and in addition it was provisionally agreed to apply Xn; R22. IND would provide the TC C&L with more detailed data on

Acute toxicity by oral route during the follow-up period, in case Member States did not agree to the provisionally classification they would then get the possibility to react else the provisional classification would be considered confirmed at the end of the Follow-up period. In addition SCL would apply between 5-10 % for R37.

Follow-up:

IND did provide the requested information (ECBI/79/06 Add. 4). They stated that this document clarifies the doses of ethephon used in the neurotoxicity studies and shows the lack of mortality at 2000 mg/kg ethephon pure. These additional data should help to avoid any R22 classification.

Member States were requested to react within the Follow-up period in case they agreed to deletion of R22 based on the information from IND.

BE sated that the data from the neurotoxicity studies confirmed that classification with Xn, R22 was unwarranted for ethephon pure and ethephon technical Base 250.

NL confirmed that R22 was warranted for ethephon in document ECBI/79/06 Add. 5.

DK said that they supported maintaining Xn; R22, based on the data summarised by NL.

IRL stated that they still supported the RMS's initial classification for acute oral toxicity (R22). The data from the submitted neurotox studies outlined in ECBI/79/06 were not sufficient for determining an acute LD_{50}. In their view the RMS was correct in arguing that the corrected dose levels allowing for the actual content of active substance administered in conjunction with the revised lower LD_{50} for female rats in the original validated study was sufficient justification for classification with R22.

Final Conclusion:

Since there was only one Member State opposing against Xn; R22 classification in the written procedure, and three Member States confirmed the provisionally agreed classification at the meeting (Member States was asked to react only in case they supported deletion of R22), Xn; R22 was confirmed for ethephon and a final agreement was reached by the TC C&L during the follow up procedure. The classification for ethephon would be **Xn; R20/21/22 - C; R34** (No classification for environmental end-points were agreed in January 2007), specific concentrati0on limits would be applied for **R37, i.e.: C ≥ 25%: C; R20/21/22 – 34**

10% ≤ C < 25%: C; R34

5% ≤ C < 10%: Xi; R36/37/38

the resulting labelling would be with symbol: C, R-phrases: 20/21/22-34 and S-phrases: (1/2 –) 26 –36/37/39 – 45.

ANNEX 2

Conclusions of the discussion from the TC-C&L in January 2007 (Summary record ECB/08/07) (excerpts only).

4. First discussions of existing pesticides

4.1 Pesticides reviewed under Directive 91/414/EEC

P509	**Ethephon (NL)**	015-154-00-4 EC: 240-718-3 CAS: 16672-87-0	ECBI/79/06 Add. 1 and 2

ECB reported about the proposal from NL to classify the substance as N; R51-53 which was supported in the written procedure by DK. However, UK in the written procedure had strong doubts about the applicability of R53.

UK reiterated their position not to apply R53 which would lead to no classification for the substance. **NL** said that they would agree now with UK that the substance indeed degraded within reasonable time to non-classifiable compounds. **DK** mentioned ethylene which was also breakdown product of ethephon adding that it was a hormone in higher plants not in algae. In

Lemna, would it be tested, there would be effects. **NL** responded that ethylene was discussed in this committee already and no classification was agreed.

Therefore the arguments from DK were not valid. **DK** responded that if that was really the case he agreed to no classification. **IND** added that ethylene was already discussed in 1995 and no classification was agreed and moreover in 2001 this decision was confirmed by the TC C&L.

The TC C&L agreed not to classify the substance for environmental effects.

Final Conclusion:

P509, **Ethephon (NL)**

015-154-00-4, EC: 240-718-3, CAS: 16672-87-0

Classification/ S –phrases	Toxicity	Degradation	Bioaccumulation	Escape clause
No classification	1 < L(E)C50 ≤ 10	Readily degradable (based on data)	log Kow < 3 BCF < 100	Not relevant
Specific concentration limits:	Not applicable			