27 November 2009

Substance name: Tris (2-chloroethyl) phosphate
EC number: 204-118-5
CAS number: 115-96-8

MEMBER STATE COMMITTEE SUPPORT DOCUMENT FOR IDENTIFICATION OF TRIS (2-CHLOROETHYL) PHOSPHATE AS A SUBSTANCE OF VERY HIGH CONCERN BECAUSE OF ITS CMR PROPERTIES

Adopted on 27 November 2009

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TABLES

Substance Name: Tris (2-chloroethyl) phosphate

EC Number: 204-118-5

CAS number: 115-96-8

- *The substance is identified as a CMR according to Article 57 (c) of Regulation (EC) 1907/2006 (REACH).*

Summary of how the substance meets the CMR (Cat 1 or 2), PBT or vPvB criteria, or is considered to be a substance of an equivalent level of concern

Pursuant to Annex V of Commission Regulation (EC) No 790/2009[1] tris(2-chloroethyl) phosphate will as of 1 December 2010 be listed in Table 3.2 (the list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Annex VI, part 3, of Regulation (EC) No 1272/2008[2] as toxic to reproduction category 2; R60 (May impair fertility).[3]

Therefore, this classification of the substance in Commission Regulation (EC) No 790/2009 shows that the substance meets the criteria for classification as toxic to reproduction in accordance with Article 57 (c) of REACH.

Registration number(s) of the substance or of substances containing the substance:

Not available.

[1] Commission Regulation (EC) No 790/2009 of 10 August 2009 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures (1st ATP)

[2] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.

[3] Pursuant to the 1st ATP, the classification according to Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Annex VI, part 3, of Regulation (EC) No 1272/2008 will as of 1 December 2010 be toxic to reproduction category 1B, H360F (May damage fertility).

JUSTIFICATION

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

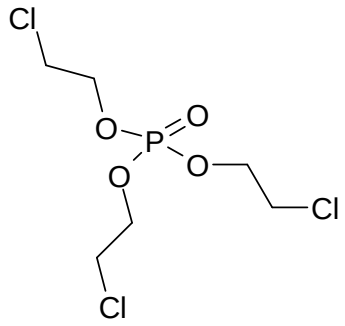
1.1 Name and other identifiers of the substance

Chemical Name:	Tris(2-chloroethyl) phosphate
EC Name:	204-118-5
CAS Number:	115-96-8
IUPAC Name:	Tris(2-chloroethyl) phosphate

1.2 Composition of the substance

TCEP is physically and not chemically bound within the polymer matrix.

Chemical Name:	Tris(2-chloroethyl) phosphate
EC Number:	204-118-5
CAS Number:	115-96-8
IUPAC Name:	Tris(2-chloroethyl) phosphate
Molecular Formula:	$C_6H_{12}Cl_3O_4P$
Structural Formula:	



Molecular Weight:	285.49 g/mol
Typical concentration (% w/w):	Degree of purity > 99.5 % (w/w)
Concentration range (% w/w):	-
Identity and percentage (w/w) of impurities:	water
Additives	-

1.3 Physico-chemical properties

Table 1: Summary of physico- chemical properties, from EU RAR (2009)

REACH ref Annex, §	Property (IUCLID 5 section)	IUCLID 5 section	Value	[enter comment/reference or delete column]
VII, 7.1	Appearance/physical state/colour	4.1	liquid	
VII, 7.2	Melting point/freezing point	4.2	< -70 °C	Akzo Nobel (10.05.2000)
VII, 7.3	Boiling point	4.3	decomposition at 320 °C at 1013 hPa	Akzo Nobel (06.07.2000)
VII, 7.4	Density	4.4	1.4193 g/cm^{3}at 25 °C	Akzo Nobel (15.06.2000)
VII, 7.5	Vapour pressure	4.6	43 Pa at 136.9 °C 0.00114 Pa at 20 °C (extrapolated)	Akzo Nobel (06.07.2000)
VII, 7.6	Surface tension	4.10	not determined	
VII, 7.7	Water solubility	4.8	7820 mg/l at 20 °C	Hazelton Europe (18.04.1994)
VII, 7.8	Partition coefficient	4.7 partition coefficient	logPow = 1.78	Hazleton Europe (20.04.1994)
VII, 7.9	Flash point	4.11	200 °C at 1013 hPa	Courtaulds Chemicals (1996)
VII, 7.12	Auto flammability	4.12	480 °C	Hoechst AG (1994)
VII, 7.10	Flammability	4.13	not extremely flammable not highly flammable not flammable	CHEMSAFE
VII, 7.11	Explosiveness	4.14	not explosive (structural reasons)	
VII, 7.13	Oxidizing properties	4.15	not oxidizing (structural reasons)	

2 CLASSIFICATION AND LABELLING

2.1 Classification in Annex VI of Regulation (EC) No 1272/2008

According to Article 57 (c) of the REACH Regulation, substances meeting the criteria for classification as toxic for reproduction category 1 or 2 in accordance with Directive 67/548/EEC may be included in Annex XIV.

Pursuant to the first ATP to the Regulation (EC) No 1272/2008 (Commission Regulation (EC) No 790/2009) as of 1 December 2010, the classification of tris(2-chloroethyl) phosphate in Annex VI, part 3, Table 3.2 of Regulation (EC) No 1272/2008 (the list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) will be as follows:

Index Number: 015-102-00-0

Classification

Carc. Cat. 3; R40 (Limited evidence of a carcinogenic effect)

Repr. Cat. 2; R60 (May impair fertility)

Xn; R22 (Harmful if swallowed)

N; R51-53 (Toxic to aquatic organisms. May cause long-term adverse effects in the aquatic environment)

Labelling

T; N

R: 60 – 22 – 40 – 51/53

S: 53 – 45 – 61

Specific concentration limits: none

According to the first ATP to Regulation (EC) No 1272/2008, the corresponding classification in Annex VI, part 3, Table 3.1 of this Regulation (EC) No 1272/2008 (list of harmonised classification and labelling of hazardous substances) will be as follows:

Index Number: 015-102-00-0

Hazard Class and Category Code(s):

Carc. 2

Repr. 1B

Acute Tox. 4 *[4]

Acute Tox. 4 *

Aquatic Chronic 2

Hazard Statement Code(s):

H351 (Suspected of causing cancer)

H360F***[5] (May damage fertility).

H302 (Harmful if swallowed)

H411 (Toxic to aquatic life with long lasting effects)

2.2 Self classification(s)

[4] Minimum classification for a category is indicated by the reference * in the column "Classification" in Table 3.1.The reference * can also be found in the column 'Specific concentration Limits and M-factors' where it indicates that the entry concerned has specific concentration limits under Directive 67/548/EEC (Table 3.2) for acute toxicity. These concentration limits cannot be "translated" into concentration limits under this Regulation, especially when a minimum classification is given. However, when the reference * is shown, the classification for acute toxicity for this entry may be of special concern.

[5] In order not to lose information from the harmonized classifications for fertility and developmental effects under Directive 67/548/EEC, the classifications have been translated only for those effects classified under that Directive. These hazard statements are indicated by the reference *** in Table 3.1.

3 ENVIRONMENTAL FATE PROPERTIES

Not relevant for this type of document.

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Not relevant for this type of document.

4.2 Acute toxicity

Not relevant for this type of document.

4.3 Irritation

Not relevant for this type of document.

4.4 Corrosivity

Not relevant for this type of document.

4.5 Sensitisation

Not relevant for this type of document.

4.6 Repeated dose toxicity

Not relevant for this type of document.

4.7 Mutagenicity

Not relevant for this type of document.

4.8 Carcinogenicity

Not relevant for this type of document.

4.9 Toxicity for reproduction

4.9.1 Effects on fertility

4.9.2 Developmental toxicity

4.9.3 Human data

4.9.4 Other relevant information

4.9.5 Summary and discussion of reproductive toxicity

Based on available animal data tris(2-chloroethyl)phosphate (TCEP) is identified as reproductive toxicant. Treatment of mice resulted in significant impairment of reproductive success of both sexes and of male reproductive organs and of sperm parameters [EU RAR, 2009]. Therefore, TCEP is classified and labelled for its effects on fertility as **Repr. Cat. 2; R 60** according to Directive 67/548/EEC or **Repr. 1B** according to the 1st ATP of the CLP regulation (EC (No.) 1272/2008Details on reproductive toxicity: Oral administration of TCEP revealed significant impairment of reproductive capacity and fertility for both sexes during continuous breeding and for two successive generations in CD1- mice. The reproductive system of male mice appeared to be more sensitive to TCEP treatment than that of females. A significant reduction of the number of litters produced by the F0 generation, reduced pregnancy and fertility indices in the F1 generation, and reduced litter size in F0 and F1 generation. A **$NOAEL_{fertility}$** of **175 mg/kg bw/day** was derived [Mice Gulati and Chapin, 1991, cited in EU RAR,2009]. There are no human data on reproductive toxicity.

4.10 Other effects

Animal studies:

Specific endpoint studies considering neurotoxicity have been evaluated within the EU RAR , 2009 (see Chapter 4.1.2.6.1.2). Besides kidneys and liver, also the brain appeared to be one of the main sites of toxicity in animal studies after repeated oral application of tris(2-chloroethyl) phosphate (dose range 22 to 700 mg/kg bw/d in rats and up to 1500 mg/kg bw/d in mice). A dose- and sex-dependent (more severe in female rats) neuronal necrosis in the hippocampal and thalamal region of the brain was observed. The NOAEL for brain effects (hippocampal lesions) was established to be 44 mg/kg bw/day in F344 rats (NTP 1991; Matthews 1993). In an acute delayed neurotoxicity study with White Leghorn hens no evidence of neurotoxicity could be observed after two oral administrations (day 1 and 3 weeks later) of 14.2 g/kg bw/day TCEP (Stauffer Chemical Company, 1979). Key animal studies considering neurotoxic effects are summarized in Table 2.

Table 2: Key studies for brain toxicity data (rats, hens) after repeated exposure to TCEP Table modified from EU RAR, 2009

Study design: Species, strain (male/female) Exposure route Exposure duration Dose	Non-neoplastic effects (selected) at LOAEL NOAEL	Reference

F344/N rat (10m/10f) Oral Gavage 16/18 weeks (f/m), 5 d/wk 0, 22, 44, 88, 175, 350 mg/kg bw/d	350 mg/kg bw/d: mortality: 4/10 (m), 3/10 (f) periodic convulsion during week 12 (f) ↑** liver and kidney weights, rel (m) ↓ brain, thymus, abs (f) neuronal necrosis, loss of neurons in the brain (f:10/10; m: 2/10) ≥175 mg/kg bw/d: in the brain: neuronal necrosis (10/10 f) loss of neurons (8/10 f) **↓** serum cholinesterase activity (f)** ≥44 mg/kg bw/d: ↑** liver and kidney weights, rel (f) $NOAEL_{sys}$ for brain lesions: (m): 175 mg/kg bw/d (f): 88 mg/kg bw/d	NTP, 1991 Matthews, 1990
F344/N rat (10m/10f) Oral Gavage 66 weeks (interim sacrifice), 5 d/wk 0, 44, 88 mg/kg bw/d rat	88 mg/kg bw/d: ↓** AP (f), ↓** ALAT (f) ↑** liver and kidney weights, rel (m) renal tubule adenoma (1/10m) brain: local necrosis, accumulation of inflammatory cells, reactive gliosis, endothelial hypertrophy (3/10 f) $NOAEL_{sys}$ for brain lesions (f): 44 mg/kg bw/d	NTP, 1991 Matthews, 1993
F344/N rat (60m/60f) Oral Gavage 103 weeks, 5 d/wk 0, 44, 88 mg/kg bw/d rat	88 mg/kg bw/d: ↓** survival (m/f); ↑** focal hyperplasia of tubule epithelium of the kidney (m:24/50; f: 16/50) ↑** degenerative lesions in the brain (f) ↑ lesions in the brain (m) 44 mg/kg bw/d: ↑** focal hyperplasia of tubule epithelium of the kidney (m:2/50; f: 3/50) $LOAEL_{sys}$ for kidney lesions (m/f): 44 mg/kg bw/d $NOAEL_{sys}$ for brain lesions (m/f): 44 mg/kg bw/d	
White Leghorn Hens (18 test animals, 10/negativ and 10/positiv control group) Oral by stomach tube 2 treatments (on day 1 and again 3 weeks later) 0, 14200 mg/kg bw	14200 mg/kg bw: mortality (4/18) ↓** body weight cessation of egg production feather loss NOAELsys: not derived	Stauffer Chemical Company, 1979

↑**: statistically significant increase compared with controls ($p<0.01$);↑ increase compared with controls, no statistically significant but possibly of toxicological relevance; ↓**: statistically significant decrease compared with

controls ($p<0.01$); m: male; f: female; AP: Alkaline phosphatase; ALAT: Alanine aminotransferase; $LOAEL_{sys}$: lowest observed adverse effect level for systemic effects; $NOAEL_{sys}$: no observed adverse effect level for systemic effects

Study not included in the EU RAR, 2009

Female Fisher-344 rats (age 75 days) were exposed to 275 mg/kg of TCEP by gavage (Tilson et al., 1990). A single exposure to TCEP results in a severe and specific pattern of damage to hippocampal neurons. Most pronounced was the damage to cells of the CA1 hippocampal pyramidal cells with lesser damage to CA4, CA3, and CA2 pyramidal cells. TCEP – induced seizures following a characteristic time-dependent pattern including wet-dog shakes, facial twitching, myoclonic motions of the jaws, forelimb clonus, and whole body jerks. Exposed rats were impaired in performing a repeated acquisition task in the water maze. A single dose of TCEP caused deficits in learning up to 3 weeks after exposure, Additional treatment with atropin and chlordiazepoxide showed a protective (seizure-related and neurohistological) effect.

Effects on humans:

One case study for human TCEP exposure has been mentioned within the EU RAR, 2009. A five year old girl developed neurogenic defects after TCEP exposure (sleeping room equipped with wood panelling treated with 3% TCEP). Shortly after the house was renovated, the clinical status improved.

A study conducted by the Austrian Umweltbundesamt (UBA 2008, Band 182) investigated the influence of indoor air pollution on children's health in nine full-time schools. Boys (n = 225) and girls (n = 224) at the age of 5 to 9 living in urban (86%) and rural (14%) environment have been included in this survey. 252 parameters (e.g. industrial chemicals, metals, volatile organic carbons) have been analyzed in air, house dust and particulate matter. TCEP was measured in house dust (n = 19) and particulate matter PM_{10} and $PM_{2.5}$ (n = 86,). TCEP could be recovered from nearly all analyzed house dust (100%) and particulate matter samples (97% in 2006, 100% in 2007). The TCEP concentration in the household dust was in the range of 0.59 and 35 mg/kg. Cognitive skills were tested using Standard Progressive Matrices (SPM) (Spearman 1938, Raven 1938). The achieved score of the SPM test is an indicator for cognitive skills, but independent from education and socio-cultural environment. Interestingly, a high correlation was found between TCEP concentration in PM_{10}, $PM_{2.5}$ and house dust and the decline of cognitive skills (-0.69, -0.68, -0.73, n = 436, boys: girls = 50%:50%, study participation = 73.1%). However, confounding factors such as spending too much time in front of the television or lack of encouragement where not considered.

Summary:

Specific endpoint studies considering neurotoxicity have been evaluated within the EU RAR, 2009 (see Chapter 4.1.2.6.1.2). Besides kidneys and liver, also the brain appeared to be the main target organ of toxicity in animal studies after repeated oral application of tris(2-chloroethyl) phosphate (dose range 22 to 700 mg/kg bw/d in rats and up to 1500 mg/kg bw/d in mice). A dose- and sex-dependent neuronal necrosis in the hippocampal and thalamal region of the brain was observed, which was more severe in female rats compared to male rats. The **NOAEL** for **brain** effects (hippocampal lesions) was established to be **44 mg/kg bw/day** in F344 rats (NTP 1991; Matthews 1993). TCEP was administered orally for 103-weeks. In an acute delayed neurotoxicity study with White Leghorn hens no evidence of neurotoxicity could be observed following two oral administrations (day 1 and 3 weeks later) of 14.2 g/kg bw/d TCEP (Stauffer Chemical Company,

1979). One case study for human TCEP exposure has been mentioned within the EU RAR, 2009. A 5 year old girl developed neurogenic defects after TCEP exposure (sleeping room equipped with wood panelling treated with 3% TCEP). Shortly after the house was renovated, the clinical status improved. In a study conducted by the Austrian Umweltbundesamt (UBA 2008, Band 182 refer to Chapter 1.4.1.1.) a high correlation between TCEP concentrations in particulate matter (indoor: PM_{10}, $PM_{2.5}$) and house dust and the decline of cognitive skills of children has been obtained.

5 ENVIRONMENTAL HAZARD ASSESSMENT

Not considered for this type of document.

6 PBT, VPVB AND EQUIVALENT LEVEL OF CONCERN ASSESSMENT

6.1 Comparison with criteria from annex XIII

6.2 PBT/vPvB Assessment/Assessment of substances of an equivalent level of concern

Neurological effects of TCEP have been shown in various studies. These are summarised in Section 5.10.

6.3 Conclusion of PBT and vPvB or equivalent level of concern assessment

REFERENCES

Literature

Note that no re-evaluation was conducted of those references which are cited in this support document and which were taken from the Risk Assessment Report for TCEP (EU RAR, 2009). The last full literature survey for the RAR was carried out in 2006 (human health and environmental part) with subsequently conducted targeted searches. For the present support document no comprehensive literature survey was carried out, but focus was given to exposure related data (especially monitoring data).

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