Annex VI Report

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: Tris[2-chloro-1-(chloromethyl)ethyl] phosphate (TDCP)

EC Number: 237-159-2

CAS Number: 13674-87-8

Submitted by: Ireland

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PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: Tris[2-chloro-1-(chloromethyl)ethyl] phosphate (TDCP)

EC Number: 237-159-2

CAS number: 13674-87-8

Registration number (s): Not applicable

Purity: 93 – 99.9% pure (w/w)

Impurities: 0.1 – 7% w/w.

There are a number of impurities which are stated as confidential by the manufacturers. This information has been presented in a confidential identity annex which has been submitted separately to ECHA.

Proposed classification based on Directive 67/548/EEC:

Carcinogen Category 3; R40

Proposed classification based on Regulation EC 1272/2008:

Category 2 Carcinogen with hazard statement H351

Proposed labelling:

Directive 67/548/EEC: Xn; R40; S(2)-36/37

Proposed specific concentration limits (if any):

None

Notes (if any):

None

The classification proposal is based on the properties of the substance itself. This dossier reviewed the carcinogenicity, mutagenicity and reproductive toxicity (male fertility and developmental toxicity) endpoints. Female fertility was not evaluated as no data are available. No classification is proposed for the mutagenicity and reproductive toxicity endpoints.

JUSTIFICATION

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Chemical Name:	Tris[2-chloro-1-(chloromethyl)ethyl] phosphate
EC Name:	tris[2-chloro-1-(chloromethyl)ethyl] phosphate
CAS Number:	13674-87-8
IUPAC Name:	Tris(1,3-dichloropropan-2-yl) phosphate
Synonyms	TDCP: this common acronym is used throughout this report Tris[2-chloro-1-(chloromethyl)ethyl] phosphate 2-Propanol, 1,3-dichloro-, phosphate (3:1) Tris(1,3-dichloro-2-propyl) phosphate Tris(1-chloromethyl-2-chloroethyl) phosphate 1,3-Dichloro-2-propanol phosphate (3:1) Phosphoric acid, tris(1,3-dichloro-2-propyl)ester Fyrol FR-2 Tolgard TDCP LV Tris CP

1.2 Composition of the substance

Chemical Name:	Tris[2-chloro-1-(chloromethyl)ethyl] phosphate
EC Number:	237-159-2
CAS name:	2-Propanol, 1,3-dichloro-, phosphate (3:1)
IUPAC Name:	Tris(1,3-dichloropropan-2-yl) phosphate
Molecular formula:	$C_9H_{15}Cl_6O_4P$
Structural formula:	O ClCH$_2$ CH$_2$Cl O–P–O ClCH$_2$ O CH$_2$Cl ClCH$_2$ CH$_2$Cl
Molecular weight:	430.91
Typical concentration:	93 – 99.9 % w/w

Chemical Name:	Confidential Impurities
Typical concentration:	0.1 – 7 % w/w

There are a number of impurities which are stated as confidential by the manufacturers. This information has been presented in a confidential identity annex which has been submitted separately to ECHA. The structures of the impurities do not suggest that they would have had a strong influence on any of the test results and will not influence the classification and labelling. No additives are used.

1.3 Physico-chemical properties

Table 1.1: Summary of physico- chemical properties

REACH ref Annex, §	Property	IUCLID section	Value	Comment/reference
VII, 7.1	Physical state at 20°C and 101.3 KPa	3.1	Liquid	
VII, 7.2	Melting/freezing point	3.2	< -20°C**	Cuthbert and Mullee, 2002a.
VII, 7.3	Boiling point	3.3	~326°C** (decomp.)	Boiled with decomposition. Cuthbert and Mullee, 2002a.
VII, 7.4	Relative density	3.4 density	1.513 at 20°C**	Cuthbert and Mullee, 2002a,
VII, 7.5	Vapour pressure	3.6	5.6×10^{-6} Pa at 25°C **	The result is consistent with the chemical structure of the main component and the other properties, in particular the boiling point. Tremain, 2002.
VII, 7.6	Surface tension	3.10		No study available, but based on the chemical structure and physico-chemical properties, TDCP not expected to exhibit surface activity.
VII, 7.7	Water solubility	3.8	18.1 mg/l at 20°C**	Cuthbert and Mullee, 2002b.
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7 partition coefficient	3.69 ± 0.36**	Cuthbert and Mullee, 2002b.
VII, 7.9	Flash point	3.11		No closed cup result is available. Read-across from TCPP (HSA/EA, 2008b), suggests that the result is likely to be above 245^0C.
VII, 7.10	Flammability	3.13		Based on the chemical structure and physico-chemical properties, TDCP is not expected to be flammable.
VII, 7.11	Explosive properties	3.14		Based on the chemical structure and the known synthetic route of manufacture via an exothermic reaction, TDCP is not expected to be explosive.
VII, 7.12	Self-ignition temperature		513 °C	Akzo Nobel, 2000.
VII, 7.13	Oxidising properties	3.15		Based on the chemical structure and analogy to

REACH ref Annex, §	Property	IUCLID section	Value	Comment/reference
				similar existing chemicals, TDCP is not expected to be oxidising.
XI, 7.17,	Viscosity	3.22	1,800 cP at 25 °C 2,200 cP at 0 °C 540 cP at 40 °C	Akzo Nobel, 2003, cited in USEPA, undated.
	Henry's law constant		1.24 x 10^{-04} $Pa.m^3/mol$ at 25°C	By calculation from VP and WS results.

Studies marked ** were performed with a composite sample of purity 94.2%, derived from recent representative commercial products from the main producers

TDCP is structurally similar to two other chlorinated alkyl phosphate esters, TCPP (Tris (2-chloro-1-methylethyl) phosphate) and TCEP (Tris (2-chloroethyl) phosphate). The structures and the key physical chemical properties of each are presented in Table 1.2 below.

Table 1.2: Structures and key physico- chemical properties for TDCP, TCPP and TCEP

	Tris [2-chloro-1-(chloromethyl)ethyl] phosphate (TDCP)	**Tris (2-chloro-1-methylethyl) phosphate (TCPP)****	**Tris (2-chloroethyl) phosphate (TCEP) ***
Structure			
Molecular weight	430.91	327.57	285.49
Physical state	Liquid	Liquid	Liquid
Melting point	<-20 ^{0}C	<-20 ^{0}C	<-70 ^{0}C
Boling point	Ca. 326 0C (decomp)	Ca. 288 0C (decomp)	320 0C (decomp)
Relative density	1.513	1.288 at 20 0C	1.4193 at 25 0C
Vapour Pressure	5.6 x 10-6 Pa at 25 ^{0}C	1.4 x 10-3 Pa at 25 ^{0}C	1.14 x 10-3 Pa at 20 ^{0}C (extrapol.)
Water solubility	18.1 mg/l	1080 mg/l at 20 ^{0}C	7820 mg/l at 20 ^{0}C
Log Kow	3.69 ± 0.36	2.68 ± 0.36	1.78

* taken from BAUA, 2006

** taken from HSA/EA 2008b

Although the structures and physiochemical properties of the three substances are considered to be sufficiently comparable to support a possible read- across, there are some differences in the target organs and critical effects for the three substances which do not support a direct read-across from data on either TCEP or TCPP.

2 MANUFACTURE AND USES

Not relevant for this dossier.

3 CLASSIFICATION AND LABELLING

The substance is not currently classified in Annex VI of Regulation No. 1272/2008.

4 ENVIRONMENTAL FATE PROPERTIES

Not relevant for this dossier

5 HUMAN HEALTH HAZARD ASSESSMENT

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

The following information on toxicokinetics is included as supporting information only. Further information can be found in the IUCLID file for TDCP.

Absorption

Following oral administration of radiolabelled TDCP to rats, absorption from the GI tract was found to be > 90 %, and therefore 100% oral absorption is assumed. No data are available for the inhalation route and in accordance with the default values given in the TGD[1], 100 % absorption via the inhalation route is assumed. An *in vitro* percutaneous absorption study using human skin membranes was conducted to determine the absorption following topical application of [^{14}C]-TDCP. The skin membranes were exposed to TDCP for 8 hours, mimicking a normal working day. The mean total absorption was 15.4 %, 10.69 % and 6.0 %, for doses 0.003, 0.01 and 0.12 mg/cm^2, respectively (HSA/EA, 2008a).

Distribution

There was no apparent effect of the route of administration on tissue distribution following oral and i.v. administration, with tissue/blood ratios for the total radioactivity similar for all tissues. Highest levels of radioactivity were found in the liver, kidney and lung following oral, dermal and i.v. administration. Tissue concentrations of either the parent compound or metabolites were low due to rapid elimination (HSA/EA, 2008a).

Metabolism

In vitro, mixed function oxidases (MFO) in microsomes of rat liver homogenate appear to play an important role in the metabolism of TDCP. The metabolite bis(1,3-dichloroisopropyl)hydrogen phosphate accounted for 75% of the MFO-metabolised TDCP. TDCP was also shown to be metabolised by glutathione-S-transferase present in the soluble fraction of rat liver, and it appears that TDCP is directly conjugated with glutathione. In a separate *in vitro* study, the metabolism of TDCP in the soluble fraction resulted in almost exclusively in one metabolite, which is possibly a γ-glutamylcysteinyl conjugation product of the parent TDCP. The following metabolites were also

[1] Technical Guidance Document in support of Commission Directive 93/67/EEC on Risk Assessment for new notified substances, Commission Regulation (EC) No 1488/94 on Risk Assessment for existing substances and Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market.

generated by the microsomal fraction of liver homogenate: bis(1,3-dichloro-2-propyl) phosphate (64 % of total metabolites), 1,3-dichloro-2-propanediol (20%), 1,3-dichloro-2-propanol (5.7 %) and an unknown metabolite (11 %).

Following i.v. administration of TDCP to rats, the metabolites isolated from rat urine were bis(1,3-dichloro-2-propyl) phosphate (67.2 % of total urine radioactivity), an unidentified polar metabolite (32 %), 1,3-dichloro-2-propyl phosphate (0.29 %) and un-metabolised TDCP (0.45 %). (HSA/EA, 2008a)

Excretion

Elimination of TDCP was rapid. Following oral administration, recovery of radioactivity after 168 hours was urine (43.2 %), faeces (39.2 %), expired air (16.24 %) and carcass (2.51 %). The decrease in radioactivity in all tissues was biphasic. The longest $t½$ was recorded in adipose tissue in both phases of elimination (17.8 and 92.4 hours, respectively).

Following i.v. administration, approximately 34 %, 20 % and 20 % of total radioactivity was excreted in the urine, faeces and expired air, respectively. The half-life of TDCP clearance in tissues was between 1.5 and 5.4 hours (HSA/EA, 2008a).

5.2 Acute toxicity

TDCP has a low acute toxicity, with an oral LD_{50} (rat) greater than 2000 mg/kg bw. The dermal LD_{50} (rat) following occluded contact for 24 hours, is greater than 2000 mg/kg bw. For inhalational exposure, the 4 hour LC_{50} (rat) is greater than 5.22 mg/l. (HSA/EA., 2008a).

No classification for acute toxicity is proposed and the above information is included as supporting information only. Further information on this endpoint can be found in the IUCLID file for TDCP.

5.3 Irritation

Skin and eye irritation have not been evaluated as part this dossier. Information on this endpoint can be found in the IUCLID file for TDCP.

5.4 Corrosivity

Corrosivity has not been evaluated as part this dossier. Information on this endpoint can be found in the IUCLID file for TDCP.

5.5 Sensitisation

Skin and respiratory sensitisation have not been evaluated as part of this dossier. Information on these endpoints can be found in the IUCLID file for TDCP.

5.6 Repeated dose toxicity

In a 2-year carcinogenicity study in which groups of 60 male and 60 female rats were fed diets containing TDCP to achieve dose levels of 0, 5, 20 and 80 mg/kg/day for 24 months, significantly greater mortality was recorded for high dose males. There was a clear adverse effect on body weight in the 80 mg/kg/day groups throughout the study, with body weights at termination >20 % lower than controls. A significant reduction in red blood cell parameters was noted for high-dose animals. Absolute and relative kidney, liver and thyroid weights were also increased in mid- and

high-dose animals. A LOAEL of 5 mg/kg/day (based on the hyperplasia, considered a pre-neoplastic lesion, observed in the kidneys in all treated groups and the testicular effects observed at this dose) can be derived from this study.

In a 90-day study to investigate the possible neurotoxicity of TDCP in hens, doses of 0, 4, 20 and 100 mg/kg/day TDCP were administered to hens. There were no mortalities in TDCP-treated birds. Under the conditions of the test, there was no evidence of TDCP induced delayed neurotoxicity. In an epidemiology study carried out in a TDCP manufacturing plant as an adjunct to a mortality study, no adverse health effects linked to TDCP exposure were determined. No data are available on inhalation and dermal repeated dose toxicity (HSA/EA, 2008a)

Repeated dose toxicity has not been evaluated as part of this dossier and the above information is included as supporting information only. Further information on this endpoint can be found in the IUCLID file for TDCP.

5.7 Mutagenicity

5.7.1 *In vitro* data

The available *in vitro* mutagenicity data for TDCP is summarised in **Table 5.1**, below.

Table 5.1 Summary of *in vitro* mutagenicity data for TDCP

Test	Endpoint	Result	Comments	Ref.
In vitro plate incorporation assay, bacteria (Ames)	Gene mutation	Non-mutagenic	Test substance: TDCP: LV. Purity not stated	SafePharm Labs (1984 & 1985b)
In vitro plate incorporation assay, bacteria (Ames)	Gene mutation	Non-mutagenic	Studies did not meet current regulatory stds Test substance: Fyrol FR-2. Purity not stated	Stauffer Chem. Co. (1976 & 1977a)
In vitro plate incorporation assay, bacteria (Ames)	Gene mutation	Significant positive response at 500 µg/plate +S9 (TA 100)	Test substance: Fyrol FR-2. Purity 95.7%	Stauffer Chem. Co. (1983a)
Ames modified quantitative suspension assay	Gene mutation	Mutagenic only at toxic doses (>1000µg/plate (+&-S9)	Not a true positive response Test substance: Fyrol FR-2. Purity 95.7%	Stauffer Chem. Co. (1983a)
Ames assays	Gene mutation	Positive response +S9 in strains TA 100 & 1535 from 333 µg/plate.	Dose-related response (Interlaboratory comparison) Test substance: Tris(1,3-dichloro-2-propyl)phosphate. Purity 94.4%	Mortelmans *et al.* (1986)

Test	Endpoint	Result	Comments	Ref.
Ames assays	Gene mutation	Weakly mutagenic +S9 with TA 100. Positive in 6 independent expts + PB-induced S9. Positive in 2 expts + PCB-induced S9 and in 3 expts +PB-induced S9. Confirmatory results with PCB-induced mouse & guinea pig liver S9.	Dose dependency observed in multiple assays Test substance: Fyrol FR-2. Purity not stated	Gold *et al.* (1978)
Ames (Pour plate assay)	Gene mutation	Weakly mutagenic + S9 with TA 100.	Test substance: TDCP. Purity not stated	Lynn *et al*. (1981)
Ames assay	Gene mutation	Positive at 0.5mg/ml +S9.	Test substance: Tris-dichloropropylphosphate. Purity not stated	Ishidate (1983)
In vitro plate incorporation assay, bacteria (Ames)	Gene mutation	Positive mutagenic response +S9 with TA 100 at 500 µg/plate	Test substance: Tris-CP. Purity not stated	Soderland *et al*. (1985)
In vitro plate mutagenicity assay, fungi (	Gene mutation	Non-mutagenic in *Sacc. cereviseriae*	Test substance: Fyrol FR-2. Purity not stated	Stauffer Chem. Co. (1976 & 1977a)
In vitro mouse lymphoma assay with L5178Y cells	Gene mutation	Positive +S9 at >80µg/ml. Non-mutagenic -S9.	Clear dose-related increase Test substance: TDCP LV. Purity not stated	Inveresk (1985)
In vitro chromosome aberration assay	Chromosome aberration	Negative with or without S9	Test substance: Fyrol FR-2. Purity not stated	Covance (2004)
In vitro mouse lymphoma assay	Gene mutation	Negative with or without S9	Test substance: Fyrol FR-2. Purity not stated	Stauffer Chem. Co. (1977b)
Sister chromatid exchange assay (L5178Y $TK^{+/-}$ cells)	SCE	Negative	Test substance: Fyrol FR-2. Purity not stated	Stauffer Chem. Co. (1977b)
Chromosome aberration assay (L5178Y $TK^{+/-}$ cells)	Chromosome aberration	Increase at highest dose analysed (118 µg/ml) +S9.	Considered equivocal. Test substance: Fyrol FR-2. Purity not stated	Stauffer Chem. Co. (1977b)
Chromosomal aberration assay	Chromosome aberration	Positive +S9 at 0.5 mg/ml	Test substance: Tris-dichloropropylphosphate. Purity not stated	Ishidate (1983)
Sister chromatid exchange (CECT assay)	SCE	Negative	Test substance: Fyrol FR-2. Purity not stated	Bloom (1982 & 1984)
In vitro transformed foci in BALB/3T3 cells	Cell transformation	Negative	Test substance: Fyrol FR-2. Purity not stated	Stauffer Chem Co. (1978b)
In vitro point mutation assay in V79 cells	Gene mutation	Negative	Test substance: Tris-CP. Purity not stated	Soderland *et al*. (1985)
In vitro UDS assay	DNA damage & repair	Minimal response at 0.1mM	Not possible to quantify response Test substance: Tris-CP. Purity not stated	Soderland *et al*. (1985)

Test	Endpoint	Result	Comments	Ref.
In vitro transformation assay in Syrian hamster embryo cells	Cell transformation	Positive at 20 & 30µM	Test substance: Tris-CP. Purity not stated	Soderland *et al*. (1985)
In vitro Salm. typhimurium mutagenicity assay with hepatocyte activation	Gene mutation	Small increase in revertants at 0.05 mM (non-induced rat livers). No increase using PB-induced hepatocytes	Test substance: Tris-CP. Purity not stated	Soderland *et al*. (1985)

5.7.2 *In vivo* data

The available *in vivo* mutagenicity data for TDCP is summarised in **Table 5.2** below.

Table 5.2 Summary of *in vivo* mutagenicity data for TDCP

Test	Endpoint	Result	Comments	Ref.
In vivo Mouse micronucleus assay	Clastogenicity	Non-clastogenic	Test substance: Tolgard TDCP LV. Purity not stated.	SafePharm Labs Ltd. (1985)
In vivo Mouse bone marrow cytogenetic assay	Chromosome aberration	Non-clastogenic	Test substance: Fyrol FR-2. Purity not stated,	Stauffer Chem Co. (1978c)
In vivo/in vitro urine mutagenicity assay	Mutation	Negative	Test substance: Fyrol FR-2. Purity not stated,	Stauffer Chem Co. (1978d)
In vivo/in vitro unscheduled DNA synthesis assay	DNA damage & repair	Negative	Test substance: TDCP. Purity >99% w/w	Covance Laboratories Inc. (2005)
Recessive lethal mutation assay in Drosophila	Chromosomal mutation	Negative	Test substance: Fyrol FR-2. Purity not stated,	Stauffer Chem Co. (1978e)

5.7.3 Human data

No data available for this dossier.

5.7.4 Other relevant information

No data available for this dosser.

5.7.5 Summary and discussion of mutagenicity

No data from humans are available on the mutagenicity of TDCP.

There is evidence to suggest that TDCP is mutagenic *in vitro*. Positive results were obtained in tests for gene mutation in both bacterial cells (Ames test) and mammalian cells (mouse lymphoma L5178Y) in the presence of metabolic activation. TDCP also caused an increase in the occurrence of chromosome aberrations in mouse lymphoma cells in the presence of metabolic activation, although a chromosome aberration study in CHO cells did not induce an increase in chromosome aberrations or polyploidy.

In vivo, TDCP was not clastogenic in a mouse micronucleus assay conducted to OECD Guideline 474. TDCP was found not to induce unscheduled DNA synthesis in an *in vivo/ in vitro* UDS assay

conducted to OECD Guideline 486. Negative results were also obtained in a mouse bone marrow cytogenetic assay and in an *in vivo*/*in vitro* urine mutagenicity assay.

Therefore, as the endpoints of gene mutation (UDS test) and clastogenicity (micronucleus test) have been investigated *in vivo* and negative results obtained, it is considered that TDCP is not genotoxic *in vivo* and **no classification for mutagenicity** is proposed.

5.8 Carcinogenicity

5.8.1 Carcinogenicity: oral

Groups of 60 male and 60 female Sprague Dawley rats were fed diets containing TDCP (Fyrol FR-2, purity 95% w/w) to achieve dose levels of 0, 5, 20 and 80 mg/kg/day of TDCP for 24 months (Stauffer Chemical Company, 1981a; Freudenthal, R.I. and Henrich, R.T., 2000). All information from this study could not be located and so was not available to the submitting Member State. The reporting is also somewhat limited. All available information is reported here. 10 animals of each sex were selected for interim sacrifice at 12 months. Animals were routinely observed for morbidity, mortality and clinical signs of toxicity. Body weights and food consumption were measured and blood and urine samples taken periodically from selected animals for haematology, clinical chemistry and urinalysis. Full necropsy was carried out on all animals. Tissues from control and high dose animals were examined microscopically, as were gross lesions, tissue masses, liver, kidney and testes of low and mid dose animals.

Mortality rates in all groups were low during the first 12 months and low in most groups from 12 through to 17 months, with the exception of the high dose males where there was a slight increase in the number of deaths. After month 17, the mortality rate increased in all groups and remained high until the end of the study (this can be expected in ageing animals). Total mortality in low- and mid-dose males and in all TDCP-treated females was considered comparable to that of the controls. Significantly greater mortality ($p<0.05$) was recorded for high dose males, (38/60 and 26/60 animals died in the high and control groups, respectively).

There was a clear adverse effect on body weight at 80 mg/kg/day, throughout the study, with body weights at termination >20 % lower than control animals. Slight decreases (most differences did not exceed 5 %) in male body weights in the 20 mg/kg/day at some intervals of the study may also have been related to treatment. Food consumption for controls and high dose animals was generally comparable except for slight increases in values for the high dose groups during the last few months of the study.

Examination of the tissues from the 12-month interim group and those animals found dead prior to 12 months found an increased incidence of neoplastic nodules in the livers of rats in the 80 mg/kg/day group, which were identified as hepatocellular adenomas. There was also an increase in interstitial (Leydig) cell tumours in the testes of males at 20 and 80 mg/kg/day. The incidence of neoplasms in all other tissues was similar in control and treated animals at this time.

At 24 months, the incidence of renal cortical adenomas in males was 1/45 (2 %), 3/49 (6 %), 9/48 (19 %) and 32/46 (70 %) at 0, 5, 20 and 80 mg/kg/day, respectively (reaching statistical significance from 20 mg/kg/day). In females, the corresponding incidences were 0/49 (0 %), 1/48 (2 %), 8/48 (17 %) and 29/50 (58 %), respectively, with statistical significance again from 20 mg/kg/day. There was no reported incidence at 12 months. In addition to the tumours, there was an increase in the incidence of hyperplasia of the convoluted tubule epithelium at 24 months in females at 80 mg/kg/day and in males in all treatment groups when compared to control animals.

In the livers of male animals at 24 months, the incidence of hepatocellular adenomas was 2/45 (4 %), 7/48 (14.5 %), 1/48 (2 %) and 13/46 (28 %) at 0, 5, 20 and 80 mg/kg/day, respectively, with statistical significance reached at 80 mg/kg/day. In females, the corresponding incidences were 1/49 (2 %), 1/47 (2 %), 4/46 (9 %) and 8/50 (16 %), respectively, with statistical significance again at 80 mg/kg/day. At the 12 month interim sacrifice, the incidence of hepatocellular adenomas was 3/14 and 1/10 for males and females respectively at 80 mg/kg/day compared to none in control animals.

At 24 months, the incidence of hepatocellular carcinoma was also increased in males and females, with the incidence in males being 1/45 (2 %), 2/48 (4 %), 3/48 (6 %) and 7/46 (15 %) at 0, 5, 20 and 80 mg/kg/day, respectively, although this did not reach statistical significance. The corresponding values in females were 0/49, 2/47 (4 %), 2/46 (4 %) and 4/50 (8 %). There was no reported incidence at 12 months.

At 24 months, the incidence of Leydig cell tumours of the testes (benign tumours) was 7/43 (16 %), 8/48 (17 %), 23/47 (49 %) and 36/45 (80 %), at 0, 5, 20 and 80 mg/kg/day, respectively. The effects were statistically significant at 20 and 80 mg/kg/day. At 12 months, 3/13 mid dose animals and 3/11 high dose animals were observed to have Leydig cell tumours; no tumours were observed in control animals at 12 months.

There was also an increased incidence of adrenal cortical adenomas in high dose females at 24 months; 8/48 (17 %) in control females and 19/49 (39 %) in high-dose females; the difference being statistically significant. At 12 months the incidence was in females was 5/11 (45 %) and 1/10 (10 %) for control and high dose groups, respectively.

5.8.2 Carcinogenicity: inhalation

No studies are available.

5.8.3 Carcinogenicity: dermal

No studies are available.

5.8.4 Carcinogenicity: human data

The mortality experience of workers employed at a TDCP manufacturing plant was investigated in a retrospective cohort study of male workers who were employed for a minimum of 3 months during the 1956-77 study period and were followed through to 1980 (Stauffer Chemical Co., 1983b). Of the 289 workers eligible for the study, 50% had worked at the plant for < 5 years while 42 workers had been employed for ≥ 15 years. Ten workers died during the study period. The report indicates that all workers were exposed to 'extremely low levels of TDCP in the work environment'. Breathing zone sampling was performed between 1978 and 1981; TDCP levels were always below the limit of detection (8 ppb).

The overall mortality of the study population was 75 % of that expected in a comparable population of US males. For the category 'all causes', the SMR (observed deaths/expected deaths x 100) was 75 (no confidence interval reported). Mortality due to 'all malignant neoplasms' was slightly higher than expected with an SMR of 131. Three cases of lung cancer were observed (vs. 0.8 expected). However, the numbers were too small to calculate a p-value. One case had worked as a janitor in the plane office and was considered non-exposed. The second case had only worked at the plant 2 years prior to onset of disease and the third case had worked for 19 years, as a production operator and a mechanic. All three decedents were moderate to heavy cigarette smokers. Overall, it was

concluded that there was no evidence linking these lung cancers with TDCP exposure. This was the only elevated cancer observed. Due to the findings of liver, kidney and testicular tumours in the 2-year carcinogenicity study in rats, this study also aimed to determine whether tumours would also occur in humans at these sites. No cancers at these sites were observed.

5.8.5 Other relevant information

No data available.

5.8.6 Summary and discussion of carcinogenicity

A retrospective cohort study is available from a TDCP manufacturing plant. The study included 289 workers, who were employed at the plant for a minimum of three months during the study period of 21 years. No evidence of an increased cancer risk among the workforce was found.

There is one 2-year carcinogenicity study in rats available for TDCP. In the study, a significant increase in the incidence of renal cortical adenomas at 20 and 80 mg/kg/day was observed at 24 months. The incidence of benign testicular Leydig cell tumours was also increased at 20 and 80 mg/kg/day at both 12 and 24 months. Hepatocellular adenomas and adrenal cortical adenomas were statistically increased at 80 mg/kg/day at 24 months. A LOAEL of 5 mg/kg/day, based on increased incidence of hyperplasia of the convoluted tubule epithelium observed in all treated male animals was derived for the carcinogenicity endpoint. Hyperplasia is often considered as a pre-neoplastic lesion, which can lead to tumour formation. The study report does not provide enough detailed information to conclude whether the hyperplasia observed following treatment with TDCP would progress to cancer or whether the tumours observed with TDCP arise through a different mechanism. However, it is not unreasonable to assume that the tumours have developed through hyperplastic changes.

The mode of action of tumour formation of TDCP in the kidney, liver and adrenal glands has not been elucidated. In the testes, there was an increased incidence of Leydig cell tumours in males at 20 and 80 mg/kg/day at both 12 and 24 months. The mechanism by which TDCP induces such tumours is not known. It is reported that one non-genotoxic mode of action by which chemicals can induce such tumours is attributed to alterations in the Hypothalamus-Pituitary-Testis (HPT) Axis which results in elevated levels of luteinising hormone (LH). Increases in LH levels have been shown to be necessary for the induction of Leydig cell tumours through chronic stimulation of the Leydig cells. There are seven known non-genotoxic hormonal mechanisms which have the potential to disrupt the HPT axis leading to Leydig cell tumour induction. Two of these modes of action are not considered of relevance to humans (GnRH antagonism and dopamine agonism) (Clegg *et al.,* 1997). However, the other five mechanisms, (5 α-reductase inhibition, androgen receptor antagonism, inhibition of testosterone biosynthesis, aromatase inhibition and exogenous oestrogen agonism) have been considered to be potentially relevant to humans. In the kidney, cleavage of glutathione conjugates to reactive metabolites can lead to nephrotoxicity (Dekant, 2001). *In vitro* metabolism studies with TDCP identified a glutathione metabolite of TDCP, although it is noted that this metabolite was not present *in vivo* (HSA/EA, 2008). It is plausible, therefore, that such glutathione metabolites could be cleaved by β-lyase in the kidney to form reactive thioaldehydes, resulting in cytotoxicity and hyperplasia, leading to tumour formation.

Overall, while the mode of action by which the tumours are induced cannot be identified, there may be some concern for man regarding their formation.

In the study presented, there is evidence that the high dose group of 80 mg/kg/day may have exceeded the maximal tolerated dose (MTD), since the terminal body weights of this groups were

greater than 20 % lower than control animals and the mortality in males of this group was also significantly increased. However, the incidence of renal cortical adenomas in both sexes and Leydig cell tumours of the testes in males were significant from the mid dose group, giving a clear evidence of a tumourigenic effect in the absence of overt toxicity.

As discussed in section 5.7 above, TDCP is not considered to be genotoxic *in vivo*. This indicates that TDCP may be assumed to be a non- genotoxic carcinogen and thus act via a threshold mechanism.

Overall, based on the results from one carcinogenicity study with TDCP, where an increased incidence of tumours in the kidney, liver, testes and adrenal glands were observed, together with evidence that TDCP is not genotoxic *in vivo*, lead to a proposal for classification as **Carc. Cat. 3; R40** (Carc. 2 H351[2]). This proposal is in line with a previous provisional agreement at the TC C&L Meeting to classify TDCP as Carc. Cat 3; R40[3].

It is proposed that a higher classification, i.e. Carc. Cat 1 or Carc. Cat 2 (Carc. 1A/1B H350[2]) is not appropriate for TDCP as evidence is only available from one carcinogenicity study, conducted in one species. Although a NOAEL was not derived from the study, an increase in tumours above the spontaneous background incidence was not observed in the low dose group, possibly indicating that there is a dose response relationship for this effect. Also, TDCP may also be assumed to be a non-genotoxic carcinogen, thus warranting a lower level of concern.

5.9 Toxicity for reproduction

5.9.1 Effects on fertility

A fertility study in male rabbits was carried out using 40 male and 80 female Dutch belted rabbits (Stauffer Chemical Company, 1982b). Ten male rabbits were assigned to each of four dose groups and treated with 2, 20, or 200 mg/kg/day TDCP (Fyrol FR-2, purity 96% w/w) in Mazola oil for twelve weeks by oral gavage. Animals were examined throughout the treatment period for signs of treatment-related toxicity. During the last week of treatment, each male was mated with one female and then with the second three days later. The females were returned to their cages and sacrificed mid-gestation. The reproductive tract was removed and examined to determine the number of corpora lutea in each ovary, the number of implantation sites and viable foetuses. Males were sacrificed at the end of the mating period and the reproductive tract (testes, epididymides, spermatic cord with blood and lymphatic vessels and ductus deferens, ampullary gland, vesicular gland, seminal vesicle, prostate gland, paraprostatic gland, urinary bladder, urethra, and bulbo-urethral glands) was removed for histological examination. Sperm were taken from one epididymus and analysed for sperm concentration, motility and morphology. Viability was not measured due to the subjectivity in sample readings.

Two animals in each of the 0, 2 and 20 mg/kg/day groups and one in the 200 mg/kg/day died prior to scheduled sacrifice. These deaths were not considered treatment-related. There were no clinical signs of toxicity.

[2] Regulation 9EC) No. 1272/2008

[3] Commission Working Group on the Classification and Labelling of Dangerous Substances Meeting on the Health Effects of Pesticides, Existing Chemicals & New Chemicals November 14-18, 2005

Mating, fertility and pregnancy parameters were unaffected by treatment. There were no treatment-related effects on numbers of corpora lutea, implantations, viable foetuses or resorptions. Sperm analysis was not affected by treatment. There were no histopathological changes detected in the male reproductive tract.

There was a treatment-related increase in absolute and relative kidney (14 % and 19 %, respectively) and liver weights (18 and 23 %, respectively), in the 200 mg/kg/day males. Overall, it is considered that there is no concern for male fertility in the rabbit.

In the 2-year carcinogenicity study (Stauffer Chemical Company, 1981a; and also reported in Freudenthal, R.I. and Henrich, R.T., 2000), effects were observed on the reproductive system of the male rat. As discussed in section 5.8.1, all information from this study was not available to the Rapporteur, and therefore the reporting is somewhat limited. All available information is reported here. For some effects, only control and high dose animals were evaluated at 12 months; all animals in the control and treatment groups were evaluated at 24 months.

In animals which were killed at 24 months and which died or were killed when moribund after the 12 month interim sacrifice, gross observations noted in the male reproductive tract of animals treated at 20 and 80 mg/kg/day included various discolourations, masses/nodules, enlargement and flaccidity in the testes as well as small seminal vesicles (when compared with control animals). The corresponding testes weights were not significantly higher than control males. Histological changes were also noted in the testes, the epididymides and the seminal vesicles both in control animals and all treatment groups.

In the testes, the incidence of germinal epithelial atrophy with associated oligospermia was increased above control values in the high dose group (statistical analysis was not performed on this data) at 12 months and in the mid and high dose animals at 24 months. The incidence of sperm stasis was increased above control values (approx 11 %) at the mid and high doses (approx 23 % and 31 %, respectively, statistical analysis not performed) at 24 months. There was also an increase in the incidence of amorphous eosinophilic material in the tubular lumens and periarteritis nodosa were observed in all treated animals at 24 months. These effects on sperm stasis, the incidence of amorphous eosinophilic material and periarteritis nodosa in the testes were only reported to be observed at 24 months. The report indicated that the testes were "suitable for evaluation" at 12 months, although no result was presented in the report for this time point, so it can only be assumed that the testis were evaluated for these effects at 12 months, and that no effects were observed.

In the epididymides, oligospermia was noted in one high dose animal at 12 months. There was none noted in any control animals and the epididymides from the low and mid dose animals were not evaluated, apart from one unscheduled mid dose animal. At 24 months, 26 % of the control group showed oligospermia, with 28 %, 54 % and 79 % displaying it at the low, mid and high doses, respectively. Degenerated seminal product was observed in all animals at 24 months (this was not examined in the low and mid doses at 12 months; it can only be presumed that it was examined at the high dose at 12 months, and did not occur), with the greatest increase in the high-dose group. 19 % of the control group showed degenerated seminal product, with 22 %, 23 % and 50 % displaying it at the low, mid and high doses, respectively.

In the seminal vesicles, secretory product was decreased in the seminal vesicles of one high dose animal at 12 months (not noted in any control animals and the effect was not examined in the low and mid doses at 12 months) and in all treated animals at 24 months. At 24 months, 2 % of control animals displayed decreased secretory product, compared with 84 %, 89 % and 52 % of the low, mid and high dose animals, respectively. Atrophy of the seminal vesicles was observed in all treated animals at 24 months (30 %, 31 % and 23 % of the low, mid and high dose animals, respectively),

but not in any of the control animals. Only the control and high dose 12 month animals were examined for atrophy of the seminal vesicles; no indication was given on an effect observed in the high dose animals.

As discussed in section 5.8.1, there was an increase in Leydig cell tumours of the testes in mid and high dose animals at both 12 and 24 months in this study. Therefore, it is possible that the effects observed on the testes may be secondary to an effect of the Leydig cell tumours. Of the effects noted in the study, atrophy in seminiferous tubules is often observed adjacent to large tumours, especially Leydig cell tumours. Also, atrophy in the seminal vesicles is commonly observed in association with testicular atrophy. It should also be considered that the effects noted in the male reproductive system are mainly observed in animals at 24 months and, therefore, may be secondary to the natural ageing process of rats rather than a specific effect on the male reproductive system.

No evaluation of the female reproductive system was included in the 2-year carcinogenicity study with TDCP.

5.9.2 Developmental toxicity

Two developmental toxicity studies in rats are available for TDCP.

In the first, TDCP (Fyrol FR-2, assumed purity of 100 % w/w) was administered daily to 20 mated Sprague Dawley female rats/dose group by oral gavage from days 6-15 of gestation at 0, 25, 100 and 400 mg/kg/day (Stauffer Chemical Company, 1978f). General observations were made daily, body weights measured on days 0, 6, 11, 15 and 19 of gestation. All surviving females were sacrificed on day 19 and the dams and foetuses examined grossly. Numbers of corpora lutea, implantations, resorptions, live foetuses and dead foetuses were noted. One third of the foetuses were examined by serial whole body sectioning using Wilson's technique. The remaining foetuses were eviscerated, fixed and examined for skeletal abnormalities using alizarin red staining.

There were three mortalities at 400 mg/kg/day which may have been caused by intubation errors, as findings at necropsy were not considered indicative of treatment-related effects. Clinical signs of toxicity were marked in most animals at the high dose and consisted of urine stains, hunched appearance, salivation, alopecia, rough coat, bloody crust around the nose, thinness and depression. Some clinical signs were also noted in the mid dose group and these may have been treatment-related (alopecia, hunched appearance, rough hair coat and urine stains). There was a significant body weight loss in mid and high dose animals from days 6-11 of treatment. These treated animals lost 15.6 g and 28.9 g, respectively, when compared to untreated animals who gained 22.1 g during this period. From days 11-15, mean weight gain of mid and low dose groups was not different from control, while mean weight gains were reduced in the 400 mg/kg/day group (50% of control). The overall mean weight gain from days 0-19 was significantly reduced ($p<0.05$) at 400 mg/kg/day (56% of controls). Mean food consumption was significantly reduced to 84.8% at 100 mg/kg/day (days 7-11) and at 400 mg/kg/day to an average of 45% throughout treatment. There were no specific findings at necropsy, which were indicative of a treatment-related effect. A NOAEL for systemic maternal effects of 100 mg/kg/day can be derived from this study.

Pregnancy rates were unaffected by treatment. The mean number of corpora lutea and implantation sites and the implantation efficiencies of the treated animals surviving to day 19 of gestation were similar to or exceeded control values. At 400 mg/kg/day, the rate of resorptions was statistically significantly increased when compared to controls (14.4 % compared to 6.7 %). The foetal viability index for this dose group was statistically significantly lower than control. No increase was seen at the low or mid doses.

There was a slightly lower mean foetal weight (2.21g) and crown-rump length (3.18 cm) for the 400 mg/kg/day litters when compared to controls (2.42g and 3.35 cm, respectively) although these did not reach statistical significance (Data for mean weight and crown-rump length from two of the 100 mg/kg/day litters were removed as they appeared to be of an older gestation age). The finding of increased incidence of dilated lateral ventricles of the brain was slight and within the historical control range. There was considerable evidence of retarded skeletal development in the high dose group; incomplete ossification of intraparietal and supraoccipital, nonossified hyoid and nonossified centres in the sternebrae, nonossified centre of the sacral and caudal portions of the vertebrae, nonossified arches of the sacral vertebrae and incomplete ossification of the pubis, and nonossified centres in the metacarpals and metatarsals. Such findings are consistent with the reduced foetal weight, length and viability at this dose level and indicate developmental retardation which may be related to the maternal toxicity seen at 400 mg/kg/day. The finding of increased incidence of foetuses with angulated ribs at 400 mg/kg/day may have been related to treatment but is of unknown biological significance (no historical control data for this effect was included in the report). A NOAEL of 100 mg/kg/day can be derived for developmental toxicity, based on the statistically significant increased resorptions and the decreased foetal viability index at 400 mg/kg/day.

In a second study, (Tanaka *et al*., 1981), in which only the abstract of the study is in English, groups of 15-24 female Wistar rats were dosed orally with 0, 25, 50, 100, 200 and 400 mg/kg/day TDCP in olive oil during days 7 through 15 of gestation. At the highest dose level, 11 out of 15 dams died and toxic symptoms included piloerection, salivation and haematuria. At this dose level, maternal body weight gain and food consumption were significantly reduced when compared to control values. Maternal kidney weight was significantly increased in the mid and high dose groups when compared to controls (absolute kidney weights were increased by 8.7 % and 35.5% in the mid and high dose groups and the relative weights were increased by 12.2 % and 65.3 %, respectively).

At 400 mg/kg/day, a significant increase in foetal death occurred. As indicated above, 11 out of the 15 dams dosed at this level died. One of the remaining dams had total dead implants. The remaining 3 dams had live foetuses. The number of live foetuses from this treatment group was 22 compared to a total of 194 in the control group (all other treatment groups were comparable to the controls). The number of dead foetuses in the high dose group was 26 compared to 6 in the control group. The number of dead foetuses in the other treatment groups was comparable to controls. There was no evidence of an adverse effect of TDCP on skeletal development of the foetuses at any dose level. In postnatal examination performed at dose levels of 200 mg/kg/day and below, there was no change in the performance of the offspring in functional tests such as open field, water maze, rota rod, inclined screen, pain reflex and preyer's reflex examinations. From this study, a NOAEL of 200 mg/kg/day can be derived for both maternal and developmental toxicity based on effects observed at 400 mg/kg/day.

5.9.3 Human data

No data available for this dossier.

5.9.4 Other relevant information

The effects on male fertility have been investigated for the two structurally related substances, TCPP (tris(2-chloro-1-methylethyl) phosphate) and TCEP (tris(2-chloroethyl) phosphate). In a two-generation reproductive toxicity study with TCPP, no effects were observed on the male reproductive system (reported in HSA/EA, 2008b). For TCEP, an effect on male reproductive organ weight was noted in mice and effects on sperm parameters were observed in mice and rats (reported

in BAUA, 2006). TCEP is classified as Repr. Cat 2; R60.[4] The lack of a consistent effect on male fertility for these two substances indicates that a read-across from male fertility data on either substance to TDCP is not appropriate.

The effects on female fertility have been investigated for both TCPP and TCEP. In a two-generation reproductive toxicity study with TCPP, an increase in oestrus cycle length and a decrease in uterus weight were observed in treated females (reported in HSA/EA, 2008b). In a continuous breeding study in mice with TCEP an impairment of fertility, seen as a decrease in the number of litters produced, was observed. However, in a cross-over mating trial, pregnancy and fertility indices were lower in treated male / control females only, indicating male mice are more sensitive to TCEP treatment than female mice (reported in BAUA, 2006). In a separate study investigating vaginal cytology in mice and rats following treatment with TCEP for 18 weeks, no effect on oestrus cyclicity was observed in mice. In rats, an increase in cycle length and variations in relative frequencies of oestrus stages were observed in the low and mid dose but not the high dose, and therefore the biological significance of the effect is questionable (reported in BAUA, 2006).

Given the inconsistent effects observed on the female reproductive system with TCEP and TCPP, it is not considered appropriate to read-across from female fertility data on either substance to address any possible effects on female fertility of TDCP.

5.9.5 Summary and discussion of reproductive toxicity

No data from humans are available on the reproductive toxicity of TDCP.

In a fertility study in male rabbits, no treatment related effects on mating, fertility or pregnancy parameters were observed. Sperm analysis was not affected and there were no histopathological changes detected in the male reproductive tract.

In a 2-year carcinogenicity study in rats, an evaluation was made of the male reproductive system. Only control and high dose animals were evaluated at 12 months and no significant differences were noted at this time point. Effects were noted in the testes, epididymis and seminal vesicles in all animals at 24 months, with a trend for higher incidence in the treated groups. In this study there was an increase in Leydig cell tumours in the mid and high dose males at both 12 and 24 months. Therefore, it is possible that the effects observed on the testes may be secondary to an effect of the tumours. It is also noted that the effects noted in the male reproductive system are only observed in animals at 24 months and therefore may be secondary to the natural ageing process of rats rather than a specific effect on the male reproductive system.

No evaluation of the female reproductive system was included in the two-year carcinogenicity study with TDCP. As there are no data available for effects on female fertility, it is considered that there is a data gap for this particular endpoint in females. Therefore, no proposal for classification for effects of fertility (females) can be made.

It was previously agreed to classify TDCP as Repr. Cat 3; R62, based on the results of the 2-year carcinogenicity study and analogy with TCEP.[5] However, a further review of the results of the 2-year carcinogenicity study, where the effects on male reproductive system were noted only 24

[4] Commission Working Group on the Classification and Labelling of Dangerous Substances Meeting on the Health Effects of Pesticides, Existing Chemicals & New Chemicals March 15-18, 2005

[5] Commission Working Group on the Classification and Labelling of Dangerous Substances Meeting on the Health Effects of Pesticides, Existing Chemicals & New Chemicals November 14-17, 2005

months and which may have been secondary to tumours present, combined with the clearly negative rabbit fertility study, lead to a conclusion that there is no concern for male fertility for TDCP. There are no data available to support a classification with respect to female fertility. Therefore, **no classification for effects on fertility (males)** is now proposed.

In two developmental toxicity studies in rats, summarised above, , there was no evidence of embryotoxicity in the absence of maternal toxicity. Therefore, **no classification for developmental toxicity** is proposed.

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 dossier.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Not relevant for this type of dossier.

7 ENVIRONMENTAL HAZARD ASSESSMENT

Not relevant for this dossier.

JUSTIFICATION THAT ACTION IS REQUIRED ON A COMMUNITY-WIDE BASIS

It is proposed to classify TDCP as Carc. Cat 3; R40[6] / Carc. 2 H351[7] . Harmonised classification for carcinogens is considered a Community-wide action under Article 115 and it is recommended that the classification proposal is considered for inclusion on Annex VI of Regulation (EC) No, 1272/2008.

[6] Directive 67/548/EEC

[7] Regulation (EC) No. 1272/2008

OTHER INFORMATION

TDCP was on the 4th Priority list adopted under Council Regulation (EEC) 793/93. A risk assessment report, addressing human health and the environment was prepared by the Rapporteur, Ireland, and agreed at Technical Committee for New and Existing Substances (TC NES). For further information please refer to the risk assessment report (HSA/EA, 2008).

The classification and labelling of TDCP was discussed at TC C&L Meeting[8], where it was provisionally agreed to classify TDCP as Carc. Cat 3 R40. At this meeting, it was also provisionally agreed to classify TDCP as Repr. Cat 3, R62. During the follow-up period to this meeting, the Rapporteur revised the classification proposal to no classification for fertility, for the reasons outlined in section 5.9 above, and it was agreed that this revised proposal would be discussed at the next meeting TC C&L Meeting. However, the due to other priorities on the agenda, TDCP was never discussed.

[8] Commission Working Group on the Classification and Labelling of Dangerous Substances Meeting on the Health Effects of Pesticides, Existing Chemicals & New Chemicals, November 14-18, 2005.

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