CLH report

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: **TRICHLOROMETHYLSTANNANE (MMTC)**

EC Number: 213-608-8

CAS Number: 993-16-8

Submitted by: France

Date: December 2010

Version 2

CONTENTS

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: Trichloromethylstannane (MMTC)

EC Number: 213-608-8

CAS number: 993-16-8

Registration number (s):

Purity: 90% w/w, typical for marketed substance

Impurities: Monomethyltin trichloride is manufactured as a mixture with dimethyltin dichloride. Dimethyltin dichloride in mono/dimethyltin mixtures may range up to 10% (w/w);

Water;

Trimethyltin chloride;

Tin tetrachloride.

A classification proposal was submitted and discussed at ECB (TC C&L) for health endpoints in October 2006. Classification for health was concluded by TC C&L in September 2007 and the classification that was finally agreed in September 2007 is proposed in the present dossier. For information, discussions and conclusions of the TC C&L as reported in summary records and follow-up of the corresponding meetings are presented in Appendix I of the present report.

In agreement with article 36 (1) of CLP, only mutagenicity and developmental toxicity are proposed for harmonisation in this dossier. Acute and repeated toxicity data are displayed for information so as to provide a general toxicological profile on MMTC but are not proposed for harmonisation.

Proposed classification based on Directive 67/548/EEC criteria:

Muta. Cat. 3; R68 (agreed by TC C&L in October 2006)

Repr. Cat. 3; R63 (agreed by TC C&L in September 2007)

Proposed classification based on CLP criteria:

Hazard statements:

Muta. 2; H341

Repr. 2; H361d

Signal word: "*warning*"

Pictogram: GHS08

Proposed labelling:

R68, R63

S(2-)36/37

Proposed specific concentration limits (if any):

No specific concentration limits proposed.

Proposed notes (if any):

None

JUSTIFICATION

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

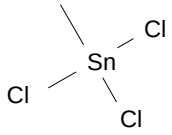
1.1 Name and other identifiers of the substance

Chemical Name:	Trichloromethylstannane (MMTC)
EC Name:	213-608-8
CAS Number:	993-16-8
CAS Name:	Stannane, trichloromethyl-
IUPAC Name:	Trichloro(methyl)stannane

1.2 Composition of the substance

Constituent

Chemical Name:	Trichloromethylstannane
EC Number:	213-608-8
CAS Number:	993-16-8
IUPAC Name:	Trichloro(methyl)stannane
Molecular Formula: CH_3Cl_3Sn	CH_3Cl_3Sn
Structural Formula:	



Molecular Weight:	240.8 g/mol
Typical concentration (% w/w):	Approx. 90%
Concentration range (% w/w):	Information not available

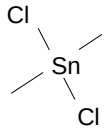
Impurities

Chemical Name:	Dimethyltin dichloride
EC Number:	212-039-2
CAS Number:	753-73-1
CAS Name	Stannane, dichlorodimethyl-

IUPAC Name: Dichloro(dimethyl)stannane

Molecular Formula: C2H6Cl2Sn

Structural Formula:



Molecular Weight: 219.67 g/mol

Typical concentration (% w/w) Approx. 10%

Concentration range (% w/w) Information not available

Classification Harmonised classification of DMTC was agreed at TC C&L in October 2006 as following:

According to 67/548/CEE	*According to CLP*
Repr. Cat. 3; R63 T+; R26 T; R25 Xn; R21 T; R48/25 C; R34	Repr. 2 – H361d Acute Tox. 2 – H330 Acute Tox. 3 - H301 Acute Tox. 3 – H311 STOT Rep. 1 – H372 Skin Corr. 1B – H314

Chemical Name: Water

EC Number: 231-791-2

CAS Number: 7732-18-5

CAS Name Water

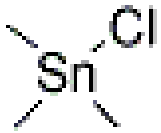
IUPAC Name: Water

Molecular Formula: H2O

Structural Formula:

Molecular Weight: 18.02 g/mol

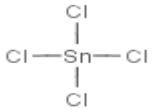
Typical concentration (% w/w)	Not known
Concentration range (% w/w)	-
Classification	No harmonised classification

Chemical Name:	Trimethyltin chloride
EC Number:	213-917-8
CAS Number:	1066-45-1
CAS Name	Stannane, chlorotrimethyl-
IUPAC Name:	Chloro(trimethyl)stannane
Molecular Formula:	C3H9ClSn
Structural Formula:	
Molecular Weight:	199.25
Typical concentration (% w/w)	Not known
Concentration range (% w/w)	-
Classification	Harmonised classification of trimethyltin chloride is set by the generic entry “Trimethyltin compounds, with the exception of those specified elsewhere in this Annex” (index 050-005-00-7 as following:

According to 67/548/CEE	*According to CLP*
T+; R26/27/28 N ; R50/53 with specific concentration limits: T+; R26/27/28: C ≥ 0,5 % T; R23/24/25: 0,1 % ≤ C < 0,5 % Xn; R20/21/22: 0,05 % ≤ C < 0,1 %	Acute Tox. 2 – H330 Acute Tox. 1 – H310 Acute Tox. 2 – H300 Aquatic Acute 1 – H400 Aquatic Chronic 1 – H410

Chemical Name:	Tin tetrachloride
EC Number:	231-588-9
CAS Number:	7646-78-8

CAS Name	Stannane, tetrachloro-
IUPAC Name:	Tetrachlorostannane
Molecular Formula:	SnCl4
Structural Formula:	



Molecular Weight:	260.5 g/mol
Typical concentration (% w/w)	Not known
Concentration range (% w/w)	-
Classification	The following harmonised classification applies:

According to 67/548/CEE	*According to CLP*
C; R34 R52-53 with specific concentration limits: C; R34: C ≥ 10 % Xi; R36/37/38: 5 % ≤ C < 10 %	Skin Corr. 1B – H314 Aquatic Chronic 3 – H412 with specific concentration limits: STOT SE 3; H335: C ≥ 5 %

Several impurities can therefore a possible influence on hazard properties and classification of MMTC depending on their concentration in MMTC.

However, the classification proposed in this dossier as displayed above does not take into account additional classifications based on impurities as impurity content can vary depending on the production process and its possible improvements.

According to articles 10 and 11 of Regulation (EC) No 1272/2008 (CLP Regulation), the potential influence of impurities on classification remains of the responsibility of the manufacturer/importer.

1.3 Physico-chemical properties

REACH ref Annex, §	Property	IUCLID section	Value	[enter comment/reference or delete column]
VII, 7.1	Physical state at 20°C and 101.3 KPa	3.1		Produced as a liquid
VII, 7.2	Melting/freezing point	3.2	ca. 43 °C	CRC Handbook, 1979
VII, 7.3	Boiling point	3.3	171 °C (1013.25 hPa)	CRC Handbook, 1979
VII, 7.4	Relative density	3.4 density	1.46 g/cm^3	Elf Atochem, 1993
VII, 7.5	Vapour pressure	3.6	1.67 hPa (25 °C)	Calculated USEPA, 2000a
VII, 7.7	Water solubility	3.8	1038.4 $g.L^{-1}$ (20°C)	Spruit and Schilt, 2003
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7 partition coefficient	-0.9	Calculated Spruit and Schilt 2003 USEPA, 2000b

Table 1: Summary of physico- chemical properties

2 MANUFACTURE AND USES

2.1 Manufacture

No data available

2.2 Identified uses

Used as an industrial intermediate in the production of other organotin chemicals.

No use known for general public.

3 CLASSIFICATION AND LABELLING

3.1 Classification in Annex I of Directive 67/548/EEC

No current classification in Annex VI of CLP regulation.

3.2 Self classification(s)

No information available.

4 ENVIRONMENTAL FATE PROPERTIES

Not covered by this dossier.

5 HUMAN HEALTH HAZARD ASSESSMENT

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

No data available for this dossier

5.2 Acute toxicity

5.2.1 Acute toxicity: oral

Species	LD_{50} (mg/l)	Observations and remarks	Ref.
Rat (500 mg/kg: 5 females 1000 mg/kg: 5/sex 1500 mg/kg: 5/sex 1750 mg/kg: 5 males)	1157.6 mg/kg bw	Test substance: MMTC:DMTC; (90:10%) Doses: 500, 1000, 1500 and 1750 mg/kg bw; observation period: 14 days after application; Mortality (deaths/animals tested): 500 mg/kg: Females, 0/5 1000 mg/kg: Males, 1/5; Females, 5/5 1500 mg/kg: Males, 3/5; Females, 5/5 1750 mg/kg: Males, 3/5 Spontaneous death occurred within 1-2 days following dosing at 1000 and 1750 mg/kg, and all deaths at 1500 mg/kg occurred on Day 1.	Elf Atochem, 1993

5.2.2 Acute toxicity: inhalation

Not covered by this dossier

5.2.3 Acute toxicity: dermal

Not covered by this dossier

5.2.4 Summary and discussion of acute toxicity

By oral route, a single acute toxicity study is available and reports a LD_{50} of 1158 mg/kg in rats for a mixture of MMTC: DMTC (90:10). DMTC is more acutely toxic that MMTC and could influence this result. In similar test conditions (same laboratory and same year), a rat oral LD_{50} of 409 mg/kg is reported for the mixture DMTC:MMTC:TMTC (84.5%:15.2%:0.5%). Based on these two studies and taking into account an approximate LD_{50} of 10 mg/kg for TMTC, it can be estimated by calculation that the LD_{50} of pure DMTC approximates 246 mg/kg and of pure MMTC 1258 mg/kg. Oral acute toxicity of the mixture MMTC:DMTC is therefore not solely explained by acute toxicity of DMTC. Information on acute toxicity is reported here for information only, so as to provide a general toxicological profile on MMTC.

This point is however not proposed for harmonisation.

5.3 Irritation

Not covered in this dossier

5.4 Sensitisation

Not covered in this dossier

5.5 Repeated dose toxicity

5.5.1 Repeated dose toxicity: oral

Species	Dose mg/kg body weight, mg/kg diet	Duration of treatment	Observations and Remarks	Ref.
Rat	30, 150, 750 mg/kg diet (equivalent to 1.9, 9.8 and 49.7 mg/kg bw/day in males and 2.1, 10.2 and 53.6 mg/kg bw/day in females)	13 weeks	Test substance: MMTC:DMTC; (82.85:9.29%) The possible sub-chronic toxicity of the test substance in rats was examined using continuous administration via the diet for 13 consecutive weeks (OECD 408). In satellite groups of female rats, a reproduction/developmental screening test (OECD 421) was performed to provide initial data on possible reproductive and developmental effects of trichloromethylstannane. The 13-week study comprised four groups of 10 rats/sex and the satellite study used four groups of 10 female rats. Male rats from the main study were mated, after a premating period, with female rats of the satellite groups which were fed the same dose of test diets. (See section 5.8.2 Developmental Toxicology) **Range Finding:** Dietary doses of 50, 250, 750, and 1500 mg trichloromethylstannane/kg feed (ppm) were administered for 14 days. The body weights were sporadically decreased in males of the 750 mg/kg group and throughout at 1500 mg/kg. Food consumption was significantly decreased in males of the 750 and 1500 mg/kg groups on day 7 and 14. Food consumption was significantly increased in females of the 50 and 250 mg/kg groups (day 7) and significantly decreased in females of the 750 mg/kg group (days 7 and 14) and the 1500 mg/kg group (day 7). Food conversion efficiency was significantly decreased in males of the 1500 mg/kg group (days 7 and 14). The absolute weights of the testes were significantly decreased in the males of the 50 and 1500 mg/kg groups. Absolute spleen weights, relative kidney weights and absolute and relative	Appel, 2004

			liver weights were significantly decreased in the males of the 1500 mg/kg group. Absolute weights of the ovaries were significantly increased in the females of the 250 mg/kg group and decreased in the females of the 1500 mg/kg group. Absolute and relative spleen weights were significantly decreased in females of the 750 and 1500 mg/kg groups. Dietary exposure of trichloromethylstannane up to 1500 mg/kg for 14 days was tolerated; however, the body weight and food consumption decreases were deemed palatability effects at 750 and 1500 mg/kg. The low food intake, low food efficiency, and organ weight effects at these doses were suggestive of a toxic response threshold. **Main Study:** **TEST SUBSTANCE INTAKE:** Overall intake of the test substance for the 30, 150 and 750 mg/kg groups was 1.9, 9.8 and 49.7 mg/kg bw/day, respectively, in males and 2.1, 10.2 and 53.6 mg/kg bw/day, respectively, in females. - Body weight gain: Similar among the groups in males and females throughout the study. - Food consumption: Similar among the groups in males throughout the study. Food consumption was slightly higher (ca. 8%) in females of the 750 mg/kg group. This difference was statistically significant during the last three weeks of the study. - Food conversion efficiency: Similar among the groups in males and females throughout the study. An occasional significant difference was seen. - Neurobehavioral testing: In animals of the 750 mg/kg diet group, some statistically significant effects were observed during neurobehavioural testing at the end of the study in week 13. In males, increases in forelimb gripstrength, landing footsplay and body temperature were measured, and a marginal effect was shown on click response. Hyperactivity was clearly observed in both males and females. The changes were considered related to treatment and toxicologically relevant. - Clinical chemistry: At the end of the treatment period the following statistically significant differences (relative to the control group) were observed: ALP: increased in males of the 750 mg/kg diet group	

			and decreased in females of the 30 mg/kg diet group; ASAT: increased in males and females of the 750 mg/kg diet group; Albumin: increased in males of the 750 mg/kg diet group; Albumin/globulin ratio: decreased in females of the 750 mg/kg diet group; Urea: increased in males of the 750 mg/kg diet group; Creatinin: increased in males of the 750 mg/kg diet group; Total bilirubin: decreased in females of the 750 mg/kg diet group; Cholesterol: increased in males of the 750 mg/kg diet group Phospholipids: increased in males of the 750 mg/kg diet group; Chloride: increased in males of the 750 mg/kg diet group; Potassium: decreased in males of the 750 mg/kg diet group. - Haematology: RBC, Hb and PVC were statistically significantly increased in females and MCV and MCH were statistically significantly increased in males of the 750 mg/kg diet group. Thrombocytes (females) and prothrombine time (males and females) were statistically significantly decreased in the 750 mg/kg diet group. Absolute and relative numbers of eosinophils were significantly decreased in females of the 750 mg/kg diet group. Haematology parameters were similar among the control, 30 and 150 mg/kg diet groups, with the exception of a statistically significantly lower number of neutrophils in males of the 30 mg/kg diet groups, which was considered a chance finding. - Urinalysis: Urinary pH and urinary crystals were statistically significantly increased in males and females of the 750 mg/kg diet group. Other semiquantitative and microscopic urinary observations were similar among the groups. - Renal concentration test: Urinary volume was statistically significantly increased and urinary density was statistically significantly decreased in males and females of the 750 mg/kg diet group. - Organ weights: The following organ weights were statistically significantly increased in the 750 mg/kg diet group:	

			· Absolute (males and females) and relative (males) adrenal weights; · Absolute and relative kidney weights (males and females). The following organ weights were statistically significantly decreased in the 750 mg/kg diet group(49.7 mg/kg bw/day males; 53.6 mg/kg bw/day females): · Absolute and relative thymus weights (males and females); · Absolute and relative brain weights (females); · Absolute and relative spleen weight (males); · Absolute and relative epidydimidal weights At microscopical examination, treatment related histopathological changes were observed in the thymus and the brain. Six males of the 750 mg/kg diet group showed a decreased cortex/medulla ratio in the thymus. This change was also present in three females. The treatment related histopathological changes in the brain consisted of loss of perikarya of neuronal cells in specific areas of the brain. All females and all but one male showed loss of perikarya in the pyramidal layer of the Hippocampus CA1/2. In addition, four males of the 750 mg/kg diet group demonstrated loss of perikarya in the piriform cortex, which was also considered related to treatment. Based on the changes in neurobehavioural parameters, haematology, clinical chemistry, urinalysis and organ weights and the associated histopathological findings in thymus and brain in animals of the 750 mg/kg diet group (49.7 mg/kg bw/day males; 53.6 mg/kg bw/day females), the NOAEL in the sub-chronic toxicity study was placed at 150 mg/kg diet (equivalent to 9.8 mg/kg bw/day in males and 10.2 mg/kg bw/day in females).	
Rat	20, 100 and 500 ppm (in feed) Estimated to be equivalent to 1.2, 6 and 30 mg/kg bw/day in males and 1, 5 and 25 mg/kg bw/day in females	13 weeks	Methyltin Trichloride : Dimethyltin Dichloride (78:22%) mixture Decreased mean body weight gain at 500 ppm (males), decreased mean specific gravity of urine from rats fed 500 ppm test substance (both sexes); decreased volume of urine at 100 ppm (males) and increased volume of urine at 500 ppm (males); increased relative kidney weight at 20 and 500 ppm (females); increased relative thymus weight at 100 ppm (females). Histopathological observations considered treatment-related included slight to moderate epithelial	TNO, 1978

			hyperplasia in the bladder (males in the 100 and 500 ppm groups; females in all treatment groups) and enlarged epithelial nuclei and foamy cytoplasm of the proximal tubules in the intercortico-medullary region of the kidneys (males and females in the 500 ppm group). The NOAEL of the methyltin mixture was less than the 20 ppm test concentration.	

5.5.2 Repeated dose toxicity: inhalation

Not covered in this dossier

5.5.3 Repeated dose toxicity: dermal

Not covered in this dossier

5.5.4 Summary and discussion of repeated dose toxicity:

Information on repeated dose toxicity by oral route is reported here for information only, so as to provide a general toxicological profile on MMTC and assist evaluation of developmental effects.

This point is however not proposed for harmonisation.

5.6 Mutagenicity

5.6.1 In vitro data

Test	Species Test system	Conc.	Metabol. activ.	Observations and Remarks	Ref.
Bacterial reverse mutation assay (OECD 471)	Salmonella typhimurium TA98, TA100, TA1535, TA1537, Escherichia coli WP2 uvrA.	62, 185, 556, 1667, 5000 µg/plate	With (liver fraction of Aroclor-1254-induced rats) and without	Test substance: MMTC (purity: 98.53%) Solvent: water Negative Mean number of revertants per plate at 0, 62, 185, 556, 1667, 5000 µg/plate: <u>TA1535 –S9:</u> 17±3, 13±4, 22±4, 21±2, 17±4, 13±4 <u>TA1535 +S9:</u> 14±5, 11±3, 11±6, 10±2, 12±4, 9±2 <u>TA1537 –S9:</u> 7±2, 6±3, 7±2, 10±7, 6±5, 4±2 <u>TA1537 +S9:</u> 10±6, 11±4, 15±2, 11±5, 6±2, 5±2	Krul, 2002

				TA98 –S9: 20±4, 26±2, 19±1, 25±3, 19±7, 15±1 TA98 +S9: 39±15, 36±7, 21±3, 44±7, 41±5, 21±3 TA100 –S9: 145±4, 134±16, 135±10, 131±9, 119±18, 83±13 TA100 +S9: 148±24, 139±22, 120±17, 142±9, 136±20, 104±27 E coli –S9: 36±5, 34±1, 32±11, 38±7, 16±7, 12±4 E coli +S9: 43±4, 42±8, 39±2, 30±1, 14±5, 16±4 Positive controls gave expected increase in revertants.	
Bacterial reverse mutation assay	Salmonella typhimurium TA100	0.1-100 µg/tube	Without	Test substance: MMTC (Source: Aldrich, purity not given) Solvent: distilled water Negative No further information given.	Hamasaki, 1993
SOS chromotest	Escherichia coli PQ37	Not reported	Without	Test substance: MMTC (Source: Aldrich, purity not given) Solvent: distilled water 4NQO was used as positive control and DMSO as negative control. The assay was carried out 6 times for each chemical and was performed at the concentration at which a decrease of the activity of alkaline phosphatase was observed or at the highest soluble dose. The SOS-inducing potency was assessed by calculation of the Induction factor (β-galactosidase units to alkaline phosphatase units) Negative The average Induction factor for 4-NOQ was 26.4±6.1. No further information available.	Hamasaki, 1992
Rec-assay	Bacillus subtilis (H17 Rec+ and M45 Rec-)	10 to 10E4 ug/50 uL	Without	Test substance: MMTC (Source: Aldrich, purity not given) Solvent: distilled water 4NQO was used as positive	Hamasaki, 1992

				control and DMSO or distilled water as negative control. The assay was carried out 4 times for each chemical. The potency to damage DNA was assessed by the difference of growth inhibition between Rec+ and Rec-. Negative 4-NOQ induced a difference of growth inhibition of 10.6±1.7 mm and DMSO or distilled water did not inhibit the growth of both strains. No further information available.	

5.6.2 In vivo data

Test	Species Test system	Conc.	Observations and Remarks	Ref.
Micronucleus assay	Rat Gavage	37, 111, 333, 1000 mg/kg (single dose)	Test substance: MMTC (purity 98.53%; DMTC 1.32%) Solvent: 0.9% sodium chloride Positive. A rat micronucleus assay, conducted according to OECD Test Guideline 474, demonstrated that methyltin trichloride (98.53% purity) produced a statistically significant increase in the number of micronucleated polychromatic erythrocytes (MPE) at dose levels of 37 mg/kg bw and above. The MPE response did not increase with increasing dose and was transient, appearing only 24 hours after treatment, but not at 48 hours after treatment. These results could be judged equivocal or characterized as weakly positive for induction of MPE from bone marrow cells in rats. Methyltin trichloride did not increase the number of polychromatic erythrocytes (PE) in the dosed animals and no clinical signs were observed. Lowest concentration at which a weak genotoxic effect was observed, was 37 mg/kg bw. Mean number of MPE per 2000 polychromatic erythrocytes in negative control, 37, 111, 333 and 1000 mg/kg MMTC and mitomycin C (1.5 mg/kg): 24h-harvest: 1.2±0.4, 3.0±1.2*, 1.8±0.4, 3.0±1.4*, 3.4±1.7*, 26.8±3.3* 48h-harvest: 2.4±1.8, -, -, 1.8±1.1, 1.6±0.9, - * $p<0.05$ (t-tests)	deVogel, 2003

5.6.3 Human data

No data available.

5.6.4 Summary and discussion of mutagenicity

In vitro, MMTC does not induce mutagenic or genotoxic effects on bacteria in Ames test, SOS chromotest on *E. coli* and rec-assay on *B. subtilis*. It should be noted that some of these tests were performed only in absence of metabolic activation.

In vivo, MMTC induces a weak and transient increase in micronuclei in a guideline study in rats by gavage. The increase was statistically significant and observed from the lowest dose level although increase is not dose-related. MMTC is therefore considered as weakly genotoxic *in vivo* and a classification Muta. cat. 3; R68 is warranted and was agreed at TC C&L of October 2006 (CLP Muta 2; H341).

It should be noted that in the *in vivo* test, MMTC contains a low proportion of DMTC. The available data suggests that DMTC is not mutagenic *in vivo* (DMTC classification proposal, 2006) and the positive response seen with MMTC can therefore not be attributed to DMTC.

5.7 Carcinogenicity

No data identified. CICADS (2006) refers to unpublished negative carcinogenicity studies for mixtures of mono- and dimethyltins in rats only available as brief summary in a secondary report. Neither the report nor the study is available to us and this endpoint is not submitted for harmonisation of classification.

5.8 Toxicity for reproduction

5.8.1 Effects on fertility

Not covered in this dossier

5.8.2 Developmental toxicity

Species	Route	Dose	Exp. time	Exp. period	Observations and Remarks	Ref.
Rats	Oral feed	30, 150, 750 mg/kg diet (equivalent to 1.2-2.1, 6.2-11.7 and 26.5-53.6 mg/kg bw/day)	Daily	ca. 5 weeks	Test substance: MMTC:DMTC; (82.85:9.29%) The possible sub-chronic toxicity of the substance in rats was examined using continuous administration via the diet for 13 consecutive weeks (OECD 408). In satellite gro ups of female rats a reproduction/ developmental screening test (OECD 421) was performed to provide initial data on possible reproductive and developmental effects of trichloromethylstannane. The main study comprised four groups of 10 rats/sex and the satellite study used four	Appel, 2004

					groups of 10 female rats (13-week study). (See section 5.5.1 Repeated dose toxicity: oral) In the satellite study female rats were fed their respective test diets beginning two weeks prior to the mating period, and continued on test diets through mating, gestation and up to PN 4or shortly thereafter. Male rats from the main study were mated after a premating period with female rats of the satellite groups. **TEST SUBSTANCE INTAKE:** The test substance intake of the female animals of the 30, 150 and 750 mg/kg dose groups was respectively: Premating period days 0-7: 1.8, 9.0 and 44.5 mg/kg bw/day days 7-14: 1.8, 8.8 and 43.9 mg/kg bw/day Gestation period GD 0-7: 1.9, 9.6 and 44.5 mg/kg bw/day GD 7-14: 2.0, 9.6 and 45.8 mg/kg bw/day GD 14-21: 1.2, 6.2 and 35.9 mg/kg bw/day Lactation period PN 1-4: 1.7, 11.7 and 26.5 mg/kg bw/day **MATERNAL TOXIC EFFECTS:** - Mortality and day of death: One animal of the 750 mg/kg group was found dead on GD 22 (i.e. 37 days after the start of exposure). The animal found dead on day 37 was necropsied. Findings included yellow patches on the liver, yellow appearance of the small intestines, haemorrhagic discharge from the vagina and a haemothorax. The haemothorax was considered to be the probable cause of death. Most probably the haemothorax was caused by severe dystocia, since at necropsy the uterus contained 12 dead fetuses. - Maternal Body weight: Increased body weight change from GD 7-14 of the females of the 30 mg/kg group, which was considered a chance finding. Mean body weights (change) of the females were	

					similar among the control, 30 and 150 mg/kg group during the entire study. Mean body weight (changes) between PN 1-4 of the 750 mg/kg group was decreased; however, no statistical significance was reached for these findings. - Food consumption: Food consumption of the female animals of the 750 mg/kg group was decreased (not statistically significantly) during the lactation period. During the premating and gestation periods food consumption of the females was similar in the control, 30, 150 and 750 mg/kg groups. - Mating index: 100, 90, 100 and 100% in the control, 30, 150 and 750 mg/kg groups, respectively. - Fertility index: 90, 80, 90 and 80% in the control, 30, 150 and 750 mg/kg groups, respectively. - Mean number of implantations: 11.2 (control group), 10.8 (30 mg/kg), 11.6 (150 mg/kg), 10.5 (750 mg/kg). - Gestation index: 89, 100, 100 and 88% in the control, 30, 150 and 750 mg/kg groups, respectively. - Number of pups born (number of litters): 90(8), 86(8), 99(9) and 50(7) for the control, 30, 150 and 750 mg/kg groups, respectively - Number of stillborn pups (number of litters): 2(1), 3(2), 0 and 2(2) for the control, 30, 150 and 750 mg/kg groups, respectively. - Live birth index: 98, 97, 100 and 96% in the control, 30, 150 and 750 mg/kg groups, respectively. - Post implantation losses [total implantation sites minus total live births at the first observation]: 13(18.6%), 16(15.3%), 5(4.7%) and 36*(42.9%) for the control, 30, 150 and 750 mg/kg groups,	

					respectively. (* p<0.001) **FETAL DATA:** - Litter size: The mean number of pups delivered per litter amounted to 11.2, 10.8, 11.0 and 7.1 for the control, 30, 150 and 750 mg/kg groups, respectively. - Litter weight: The mean pup weights and pup weight changes were similar in the treated groups when compared to the control group. - Pup mortality: 2.2, 3.5, 0 and 4% for the control, 30, 150 and 750 mg/kg groups, respectively at PN 1; 16, 25, 3 and 16% for the control, 30, 150 and 750 mg/kg groups, respectively at PN 4 (at 750 mg/kg, p<0.001 for difference in pups lost between PN1 and PN4 compared to controls). - Number viable: The viability index (PN 1-4) was 84, 75, 97 and 35% in the control, 30, 150 and 750 mg/kg groups, respectively. - Number live pups per litter: 11.0, 10.4, 11.0 and 6.9 for the control, 30, 150 and 750 mg/kg groups, respectively at PN 1; 10.6, 7.8, 10.7 and 4.2 for the control, 30, 150 and 750 mg/kg groups, respectively at PN 4. Interpretation of these data was complicated by the incidence of missing pups across groups. A variable incidence of pups "missing" after birth was recorded. The number of missing pups at PN 4 was 14 in controls (16% of pups born alive), 21 (25%) in the low-dose group, 3* (3%) in the mid-dose group and 30* (62%) in the high-dose group (*statistically different from controls). The missing pups were presumed to have been cannibalized by the dams, but it is not known if the missing pups were alive or dead. It is also not known if some pups were cannabilized prior to being counted for litter size at birth. This could account for the slightly lower number of recorded live	

					births and the slightly higher post-implantation loss in the high-dose versus controls. The reason for missing pups can not be determined on the basis of the data within the study. Missing pups could be due o a toxic behavioral effect on dams which caused a lack of, or abnormal, nurturing. No malformations were noted at any observation point for any of the missing pups and no overt behavioral effects were noted, however some other toxic effect on the pups could have caused the dam to eat them. NOAEL (prenatal toxicity): Based on the increase in post-implantation loss in the 750 mg/kg group, 150 mg/kg can be considered as a NOAEL for postnatal toxicity. NOAEL (prenatal toxicity): Based on the decrease of viability index in the 750 mg/kg group, 150 mg/kg can be considered as a NOAEL for postnatal toxicity. NOAEL (maternal toxicity): Based on the effects observed on body weight and food consumption in the 750 mg/kg group, 150 mg/kg diet (equivalent to 6.2 - 11.7 mg/kg bw/day in females) was considered to be the NOAEL for maternal toxicity.	
Rats	Oral – drinking water	12.0, 40 or 120 mg/L tin;	Females exposed for 14 days before breeding and through breeding, gestation, birth and nursing until the pups were weaned at 21 days.		Test substance: MMTC (purity not given but verified before use according to the article) Male rat pups were exposed to monomethyltin trichloride (MMTC) via their dam's drinking water throughout gestation and post partum until 21 days of age. At 11 days of age, the pups were tested for acquisition and extinction learning ability in an appetitive learning paradigm, and at 21 days for learning ability in a one trial swim escape learning test. At 11 days, pups from dams exposed to 120 mg/L Sn as MMTC displayed significantly significant increases in	Noland, 1982

				acquisition time, while all dose groups (12, 40, 120 mg/L MMTC) displayed significant decreases in extinction learning ability as compared to controls. At 21 days of age, animals exposed to 12 mg/L and 120 mg/L MMTC displayed higher escape times than controls.	
Rats Sprague-Dawley (CD-CRL) 53-54 days old	Oral-drinking water	Experiment #1 0, 10, 50, 245 ppm in water (equivalent to 1.0-1.8, 5.3-10.6 and 23.3-41.6 mg/kg bw/day) Purity of test substance 97%.	14 days pre-mating, through Day 11 post natal [ca. 7 weeks]	Test substance: MMTC (purity 97%) The possible developmental neurotoxicity of MMTC in rats was examined using continuous administration via drinking water beginning 14 days prior to cohabitation & mating through Day 21 of the post natal period. The study complied with the US EPA Developmental Neurotoxicity Test [DNT] guideline [US EPA 870.6300 which us equivalent to the OECD 426. Four groups of 30 female rats/group were used. Litters were culled to 8 males on PND1. **MATERNAL ENDPOINTS:** There were no changes in maternal Body weight throughout the study. - Number of dams delivering litters: 10 (control group), 11 (10 ppm), 11 (50 ppm), and 12 (245 ppm). Necropsy of all non-pregnant dams or dams not delivering revealed resorptions in only two control rats and one rat from the low dose group. Incidence of pregnancy, late delivery, and resorptions were not statistically different across treatment groups. **DATA ON OFFSPRING:** - Litter size: The mean number of pups per litter was: 12.5 (control group), 15.2 (10 ppm), 13.1 (50 ppm), and 13.4 (245 ppm). Litter birth weights and body weights across time were similar across treatment groups throughout the entire study. In addition, there were no differences in weights of the pups selected for each	Moser, 2005

				behavioral test. Live birth index and Viability index were not provided in the published article, but the author stated there were no differences across groups. There was any cannibalization in any group. There were no effects on any measure of growth, development, cognitive function, or apoptosis following MMTC exposure. There was a trend towards decreased brain weight in the high dose group. In addition, there was vacuolation of the neuropil in a focal area of the cerebral cortex of the adult offspring in all MMT dose groups (1–3 rats per treatment group). This is a mild neuropathological lesions observed in the offspring at PND85-90. The finding was called ”restricted” by the author and was given no weight in the overall conclusion. The finding is of uncertain biological significance and its relation to treatment was unclear. The author concluded that perinatal exposure to MMTC did not result in neurobehavioral, or cognitive deficits. The NOEL was 245 ppm [23.3-41.6 mg/kg bw], the highest dose tested.	
Rats Sprague-Dawley (CD-CRL) timed-pregnant	Oral drinking water	Experiment #2 0, 500 ppm in water (equivalent to 55.8-94.3 mg/kg bw/day) Purity of test substance 97%.	Gestation Day 6 [GD6] through Postnatal Day 21 [PND21] [ca. 5 weeks]	Test substance: MMTC (purity 97%) This experiment is a second developmental neurotoxicity assessment of MMTC in rats. MMTC was administered via drinking water from GD6 through PND21. This study complied with the US EPA and OECD Developmental Neurotoxicity Test [DNT] guidelines.Two groups [17 control and 18 treated] of female rats were used. Litters were culled to 8 [4 males and 4 females] on PND4 and weaned on PND21. **MATERNAL ENDPOINTS:** There was a significant depression of fluid intake across all but one day of treatment with MMTC at 500 ppm. This indicates that the “tolerated dose” was reached or exceeded. Only the intake measured 3 days post-parturition was not different	Moser, 2005

				than controls. During gestation, MMTC consumption was about 80–88% of control levels, and during lactation, 82–88% of control. Despite the lowered intake, body weight was not different in the treated group. All of the timed-pregnant females in the control group delivered, but two in the MMTC group did not. These rats were not evaluated for implantation sites. All of the deliveries occurred when expected. In the MMTC group, one litter was killed by the dam shortly after birth and another litter consisted of all females and was not used. Live birth index and Viability index were not provided in the published article, but the author stated there were no differences across groups. **DATA ON OFFSPRING:** - Number of pups per litter: 11.9 (control group), 12.2 (500 ppm). Body weight changes during the lactation period showed no differences except on PND11, male and female pups in the control group were different by about 4g. This was within biological variability. There were no treatment effects on body weight after weaning. Behavioral assessments included the runway task (PND11), motor activity habituation (PND17), and Morris water maze (PND 85-90 (adults)). MMTC exposure did not alter pup runway performance, motor activity, or cognitive function. The NOEL was 500 ppm [55.8-94.3 mg/kg bw], the highest dose tested.	

5.8.3 Human data

No data available

5.8.4 Summary and discussion of reproductive toxicity

In the OECD 421 screening test (Appel, 2004), an increase in post-implantation loss (43%) was reported at the highest dose. Besides, at this dose out of the 48 pups born alive 30 were "missing" and one pup was found dead at PND 4 resulting in a viability index of 35%.

The study report mentions that the dams may have cannibalized pups. This could explain both the missing pups resulting in a decreased viability index and the increase in post-implantation loss as some pups may have been cannibalized before litter size determination at birth. Indeed, cannibalization is likely to have occurred postnatally. However, it is not possible to know whether pups were eaten by the dams at birth before they were counted or whether there was a real increase of post-implantation loss.

Besides, cannibalization can reflect either an abnormal behaviour of the dams due to the neurotoxicity of MMTC or behaviour of the dams resulting from a poor health status of the pups, as the health status of the missing pups is not known. At the highest dose, it should be noted that 2 pups from 2 different litters were found dead on PND1 (vs. 2 in the control group) and 1 between PND1-4 (none in the control) although these findings may be incidental.

Maternal toxicity in this study was limited to a non-significant decrease of body weight and food consumption during lactation only and effects on the thymus in the high-dose group. Thymus is a target organ of MMTC and could indicate maternal toxicity. However, the effects were a slight non-significant increase in thymus weight whereas thymus weight was decreased in the corresponding subchronic study. Microscopic observations have identified 4 dams (vs. 2 in controls) with thymus involution but this was not consistent with microscopic observations in the subchronic study in which animals at high dose had a decreased cortex/medulla ratio. One death occurred in the high dose group. However, the probable cause of death is dystocia and could therefore not be attributed to maternal toxicity. No good evidence of maternal toxicity is therefore available in the OECD 421 study and cannibalization of the pups is therefore not understood. It should also be noted that in the control group the decrease of viable pups on PND4 (viability index of 84%) is also due to the observation of 14 "missing" pups (from 3 litters).

Effects on post-implantation loss or pup viability were not identified in two recent studies performed by EPA (Moser, 2006). These studies however focus on detection of neurodevelopmental effects and the number of implantations in the dams was not determined and post-implantation loss was not calculated. The litter size were however normal in all groups. However, in the Moser studies, MMTC was administered in drinking water whereas it was given in diet. MMTC may have different gastrointestinal absorption rates in these two vehicles that may explain the discrepancy in the results and the effects seen in the OECD 421 study can not be fully dismissed by the Moser studies. The study by Moser, 2006 also showed that MMTC induces no significant developmental neurobehavioral or cognitive deficit in the conditions of the studies.

Overall, the OCDE 421 study provides an indication of an adverse effect of MMTC on development (decreased viability and post-implantation loss) in the absence of maternal toxicity but the interpretation of the study is not clear due to postnatal cannibalization by the dams and a classification **Repro. Cat. 3 – R63** is warranted and was agreed at TC C&L of September 2007 (CLP Repr. 2 – H361d).

It should be noted that in the OECD 421 study (Appel, 2004), MMTC contains *ca.* 10% of DMTC. However, the data available on DMTC suggests that DMTC is foetotoxic with a LOAEL of 15 mg/kg and a NOAEL of 10 mg/kg in rat (DMTC classification proposal, 2006). In OECD 421 study, effects of MMTC are seen at the highest dose of *ca.* 50 mg/kg, which contains around 5 mg/kg of DMTC and the effects seen with MMTC can therefore not be attributed to DMTC.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Not covered in this dossier

7 ENVIRONMENTAL HAZARD ASSESSMENT

Not covered in this dossier.

JUSTIFICATION THAT ACTION IS REQUIRED ON A COMMUNITY-WIDE BASIS

The substance has CMR properties, i.e. mutagenicity and developmental toxicity that justify harmonising its classification and labelling.

In this aim, a classification proposal was submitted and discussed at ECB (TC C&L) for health endpoints in October 2006. Classification for health was concluded by TC C&L in September 2007 and the classification that was finally agreed in September 2007 is proposed in the present dossier.

For information, discussions and conclusions of the TC C&L as reported in summary records and follow-up of the corresponding meetings are presented in Appendix I of the present report.

In agreement with article 36 (1) of CLP, only mutagenicity and developmental toxicity are proposed for harmonisation in this dossier. Acute and repeated toxicity data are displayed for information so as to provide a general toxicological profile on MMTC but are not proposed for harmonisation.

OTHER INFORMATION

No other information relevant

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APPENDIX I

Collection of discussions of MMTC classification at ECB

For health effects, MMTC classification was first discussed at the Technical Committee of Classification and Labelling (TC C&L) in October 2006. Health classification was concluded at the TC C&L in September 2007.

Environmental effects were not discussed at ECB.

Extract from document ECBI/13/07 Rev. 2 - Draft Summary Record - Meeting of the Technical Committee C&L on the Classification and Labelling of Dangerous Substances - Arona, 4-5 October 2006

Methyltin trichloride, MMTC (F049) [2]

EC number: 213-608-8, CAS number: 993-16-8

Classification proposal : [Muta. Cat. 3; R68 - Repr. Cat. 3; R63 - Xn; R22 - C; R34 - Xn; R48/20/21/22 - N; R50/53]

ECBI/25/06 Add 1	F, differences in opinion for MMTC, MMT (EHMA) and TERP
ECBI/27/06	French C&L proposal, as prepared by IND, for MMTC

Acute toxicity:

The **TC C&L experts** agreed to classify MMTC with Xn; R22.

Corrosivity:

C; R34 was proposed. The available study was made on a mixture of 90% of DMTC and 10 % MMTC. **DE** and **BE** requested the method and wanted to take note of the fact that that we actually did not classify the substance discussed. **IND** has agreed to over classify in these cases as they do not want to do additional testing. **UK** also agreed to the reservation from D and BE.

It was agreed not to classify for corrosivity due to lack of data for MMTC specifically. The mixture tested would anyway have to be classified based on the high DMTC content.

Long term toxicity:

There were no data existing supporting Xn; R48/20/21/22 classification. It was agreed not to classify for long term toxicity due to lack of data, following the same reasoning as for corrosivity.

Reprotoxicity:

There was some evidence of developmental toxicity (Repr. Cat. 3; R63), based on data. **DE** suggested Repr. Cat. 2; R61. **FR** explained that this was a repeated dose toxicity test in which severe maternal toxicity was found, why no Repr. Cat. 2; R61 was proposed. **S** agreed to Repr. Cat. 2; R61. **IND** stressed that there was significant maternal toxicity.

N agreed that it is needed to look into the maternal toxicity in the developmental study and not in the long term study.

The developmental toxicity discussion was postponed to the next meeting, to allow MS experts to further examine the reprotoxicity data.

Mutagenicity:

Muta. Cat. 3; R68 was agreed without further discussion.

Conclusion:

The **TC C&L** agreed not to classify **Methyltin trichloride, MMTC** with C; R34 and Xn; R48/20/21/22. The TC C&L agreed to classify **Methyltin trichloride, MMTC** with **Muta. Cat. 3; R68 - Xn; R22**.

The **reprotoxicity discussion was postponed to the next meeting** to allow the experts to look once more into the data.

Extract from : Follow-up III of the meeting of the Technical Committee on Classification and Labelling in Arona, 26-28 September 2007

Methyltin compounds: **F049 [1]** **Methyltin trichloride, MMTC** **CAS: 993-16-8** **EC: 213-608-8** **Classification:** Muta. Cat. 3; R68 *Agreed 1006* Repr. Cat. 3; R63 *Agreed 0907* Xn; R22 *Agreed 1006* [N; R50/53] *To be discussed* **Labelling:** Xn R: 22-63-68[-50/53] S: (2-)36/37[-60-61] **Classification assigned in accordance with the CLP Regulation:** Muta. 2; H341 Repr. 2; H361d Acute Tox. 4; H302 [Aquatic Acute 1; H400] [Aquatic Chronic 1; H410] FR confirms that the acute tox. data are consistent with the classification shown. **F051 [2]** **Methyltin tris(2-ethylhexyl-mercaptoacetate, MMT(EHMA)** **CAS: 57583-34-3** **EC: 260-828-5**	*In October 2006* the TC C&L on the basis of the F proposal (ECBI/27/06) it was agreed to classify MMTC for mutagenicity in category 3 and with Xn; R22 for acute toxicity. It was agreed not to classify for corrosivity and repeated dose toxicity. *In October 2006* the TC C&L on the basis of the F proposal (ECBI/26/06 Rev. 1) it was agreed to classify MMT(EHMA) for mutagenicity in category 3 and with Xn; R22 for acute toxicity. It was agreed not to classify for sensitisation and repeated dose toxicity. (*In October 2006* the discussion of the classification for the two dimethyltin compounds: Dimethyltin dichloride, DMTC (EC No: 212-039-2, CAS No: 753-73-1) and Dimethyltin bis(2-ethylhexyl- mercaptoacetate, DMT(EHMA) (EC No: 260-829-0, CAS No: 57583-35-4) were concluded) **IND** gives in their paper ECBI/27/06 Add. 1 information on maternal toxicity and reprotoxicity of MMTC. Document ECBI/27/06 Add. 2 is a scientific paper on Evaluation of developmental neurotoxicity of organotins via drinking water in rats. Furthermore the following documents were sent by IND: ECBI/27/06 Add. 3 parts I, II, III and IV on reprotoxicity of MMTC as well. **S** commented by email on the reprotoxicity of MMTC (ECBI/27/06 Add. 4) and re-submitted the expert report ECBI/30/04 and the Guidelines for Developmental Toxicity Risk Assessment from the EPA (ECBI/27/06 Add. 5). **IND** sent further information requested by the TC C&L in documents ECBI/27/06 Add. 6 (I-IV) and ECBI/27/06 Add. 7 (I, II) distributed with Revision 2 of the September agenda *MS were asked to send their comments to the new information forwarded by IND within the deadlines for the September meeting.* **F** sent further comments developmental toxicity in their document ECBI/27/06 Add. 8 confirming their position to classify both substances with Repr. Cat. 3; R63.

Classification: Muta. Cat. 3; R68 *Agreed 1006* Repr. Cat. 3; R63 *Agreed 0907* Xn; R21/22 *Agreed 0907/1006* [NC for ENV] *To be discussed* **Labelling:** Xn R: [21]/22-63-68[-50/53] S: (2-)36/37[-60-61] **Classification assigned in accordance with the CLP Regulation:** Muta. 2; H341 Repr. 2; H361d Acute Tox. 4; H312 Acute Tox. 4; H302 *ENV still to be discussed* FR confirms that the acute tox. data are consistent with the classification shown.	***In September 2007*** the TC C&L agreed to classify MMTC and MMT(EHMA) with Repr. Cat. 3; R63 (Repr. 2 H361d). In addition it was agreed to classify MMT(EHMA) with Xn; R21. ⇨ **Next ATP if ENV classification is concluded.** ECB will evaluate whether to make a written procedure and ask the TC C&L Environmental experts to agree on classification for F049 (N; R50-53 proposed by FR in ECBI/27/06) and F051 (NC proposed by FR in ECBI/26/06) for environment, else the partial classification concerning the environment should be handed over for discussion at ECHA with support of an Annex XV dossier**.** **After FU II:** **A written procedure for ENV has not been made and consequently the issue of classification of these substances for environmental effects will be discussed further.** ⇨ **Hand-over to ECHA**