Committee for Risk Assessment

RAC

Annex 1

Background document

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

Dimethyltin dichloride

EC Number: 212-039-2

CAS Number: 753-73-1

CLH-O-0000001701-83-03/A1

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

30 November 2012

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Part A.

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	Dimethyltin dichloride
EC number:	212-039-2
CAS number:	753-73-1
Annex VI Index number:	-
Degree of purity:	50-99% w/w, typical for marketed substance.
Impurities:	Dimethyltin dichloride is intentionally manufactured as a mixture with monomethyltin trichloride (993-16-8). Dimethyltin dichloride content in di/monomethyltin mixtures may range from approximately 50-99% (by weight). Impurities include water (up to 50% w/w), trimethyltin trichloride (levels not defined), tin tetrachloride (levels not defined).

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation	**Directive 67/548/EEC (Dangerous Substances Directive; DSD)**
Current entry in Annex VI, CLP Regulation	Not present in the annex VI.	Not present in the annex VI.
Current proposal for consideration by RAC	Acute Tox.3; H301 Acute Tox.3; H311 Acute Tox.2 ; H330 Skin Corr.1C; H314 Repr. 2 ; H361d STOT RE1 H372 with nervous system as main target organ	T; R25 T; R24 T+; R26 C; R34 Repr. Cat. 3; R63 T; R48/25
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Acute Tox.3; H301 Acute Tox.3; H311 Acute Tox.2 ; H330 Skin Corr.1C; H314 Repr. 2 ; H361d STOT RE1 H372 with nervous system as main target organ	T; R25 T; R24 T+; R26 C; R34 Repr. Cat. 3; R63 T; R48/25

1.3 Proposed harmonised classification and labelling based on CLP Regulation and/or DSD criteria

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	None		None	Not evaluated
2.2.	Flammable gases	None		None	Not evaluated
2.3.	Flammable aerosols	None		None	Not evaluated
2.4.	Oxidising gases	None		None	Not evaluated
2.5.	Gases under pressure	None		None	Not evaluated
2.6.	Flammable liquids	None		None	Not evaluated
2.7.	Flammable solids	None		None	Not evaluated
2.8.	Self-reactive substances and mixtures	None		None	Not evaluated
2.9.	Pyrophoric liquids	None		None	Not evaluated
2.10.	Pyrophoric solids	None		None	Not evaluated
2.11.	Self-heating substances and mixtures	None		None	Not evaluated
2.12.	Substances and mixtures which in contact with water emit flammable gases	None		None	Not evaluated
2.13.	Oxidising liquids	None		None	Not evaluated
2.14.	Oxidising solids	None		None	Not evaluated
2.15.	Organic peroxides	None		None	Not evaluated
2.16.	Substance and mixtures corrosive to metals	None		None	Not evaluated
3.1.	Acute toxicity - oral	Acute Tox.3; H301	Not Applicable	None	
	Acute toxicity - dermal	Acute Tox.3; H311	Not Applicable	None	
	Acute toxicity - inhalation	Acute Tox.2 ; H330	Not Applicable	None	
3.2.	Skin corrosion / irritation	Skin Corr.1C H314	None	None	
3.3.	Serious eye damage / eye irritation	None		None	Not evaluated
3.4.	Respiratory sensitisation	None		None	Not evaluated
3.4.	Skin sensitisation	None		None	Not evaluated

3.5.	Germ cell mutagenicity	None		None	Not evaluated
3.6.	Carcinogenicity	None		None	Not evaluated
3.7.	Reproductive toxicity	Repr. 2 - H361d	Guidance currently not available	None	
3.8.	Specific target organ toxicity –single exposure	None		None	Not evaluated
3.9.	Specific target organ toxicity – repeated exposure	STOT RE1 H372 with nervous system as main target organ	None	None	
3.10.	Aspiration hazard	None		None	Not evaluated
4.1.	Hazardous to the aquatic environment	None		None	Not evaluated
5.1.	Hazardous to the ozone layer	None		None	Not evaluated

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Signal word: *"Danger"*

Pictogram: GHS05, GHS06, GHS08

Hazard statements: H301, H312, H314, H330, H361d, H372

Precautionary statements: not harmonized.

Proposed notes assigned to an entry: None

Table 4: Proposed classification according to DSD

Hazardous property	**Proposed classification**	**Proposed SCLs**	**Current classification** [1)]	**Reason for no classification** [2)]
Explosiveness	None		None	Not evaluated
Oxidising properties	None		None	Not evaluated
Flammability	None		None	Not evaluated
Other physico-chemical properties *[Add rows when relevant]*	None		None	Not evaluated
Thermal stability	None		None	Not evaluated
Acute toxicity	T; R25 T; R24 T+; R26	Not applicable	None	
Acute toxicity – irreversible damage after single exposure	None		None	Not evaluated
Repeated dose toxicity	T; R48/25	None	None	
Irritation / Corrosion	C; R34	None	None	
Sensitisation	None		None	Not evaluated
Carcinogenicity	None		None	Not evaluated
Mutagenicity – Genetic toxicity	None		None	Not evaluated
Toxicity to reproduction – fertility	None		None	Not evaluated
Toxicity to reproduction – development	Repr. Cat. 3; R63	Guidance currently not available	None	
Toxicity to reproduction – breastfed babies. Effects on or via lactation	None		None	Not evaluated
Environment	None		None	Not evaluated

[1)] Including SCLs
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Indication of danger: T+

R-phrases: R24-25-26-34-48/25-63

S-phrases: S26-28-36/37/39-45

BACKGROUND TO THE CLH PROPOSAL

1.4 History of the previous classification and labelling

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 October 2006. For information, discussions and conclusions of the TC C&L as reported in summary records of the corresponding meeting are presented in Annex I of the present report.

A new study (Ehman, 2007) has been published on developmental toxicity of dimethyltin dichloride (DMTC) since the TC C&L discussions and has been integrated in the present report.

Although it covers a different endpoint (developmental neurotoxicity), the results of this study are however consistent with the classification Repr. Cat. 3; R63 agreed by the TC C&L and proposed in the present dossier.

It is noted that no registration dossier is currently available for DMTC.

1.5 Short summary of the scientific justification for the CLH proposal

Several studies of acute **oral** toxicity were performed on rats which one (Klimmer 1971) showed a LD_{50} of 73.86 mg/kg bw. Animals showed signs of systemic toxicity within 2-3 hours of dosing and death within 24-72 hours of treatment, so a classification was proposed.

In the acute toxicity by **inhalation** (Wells Laboratories, 1975), rats exposed to the low dose experienced CNS depression. Gross findings at necropsy were observed, included blood in the lungs, heart failure, fluid in the chest cavity, dark spleen, and stomach filled with gas. A number of inhalation exposure studies to both aerosol and vapor at 1 and 4 hours were reported. An LC_{50} value of 0.115 mg/L was reported for a 4 hours aerosol exposure.

In a **dermal** study (Rush, R.E. 1993b), there were no deaths at 200 mg/kg, 4/5 males and 2/5 females died at 400 mg/kg and 4/5 males and 5/5 females died at 750 mg/kg. A variety of clinical abnormalities were observed including slight to severe dermal irritation at the site of application. This resulted in an **LD_{50} value of 404 mg/kg.**

In a **skin corrosion** study (Rush, R.E. 1993b), a positive result was obtained after one hour of application on the rabbit dermal tissue, so the test substance was considered to be corrosive.

Two **oral 90-day** studies on DMTC indicate that the main target organ is the nervous system. Deaths and severe neurological signs occurred from 75 ppm (5.2/6.7 mg/kg) in Elf Atochem 1996 and at 200 ppm (16.81/17.31 mg/kg) in Rohm and Haas 1999. Besides, neuropathological lesions were observed from the lowest dose of 25 ppm (1.6/2.2 mg/kg) in Elf Atochem 1996, so a classification is proposed.

Studies of Noda show that DMTC is toxic for the **prenatal development** of the fetus. Severe maternal toxicity occurred at the high dose (deaths, severe thymus atrophy, vaginal bleeding, tremors, convulsions, ataxia and others clinical signs of toxicity). Fetotoxic responses observed at the high dose included total litter resorptions, cleft palate, and significantly decreased fetal body weight.

The results of the two new studies of Ehman indicated that exposure to dimethyltin dichloride (DMTC) decreased fluid consumption, depressed maternal weight gain, altered the spatial learning in the Morris water maze, decreased brain weight and altered levels of an apoptotic marker (DNA fragmentation). Moreover, in one of the experiment, neuropathological lesions were observed, as mild vacuolation of the neuropil in the cerebral cortex. Besides, DMTC altered litter weight and pup growth in experiment 2.

Based on the induction of cleft palate in some but not all experiments, reduced fetal weight in presence of maternal toxicity and observation of a developmental neurotoxic potential, classification in Repr 2 is therefore proposed.

1.6 Current harmonised classification and labelling

No current harmonised classification in Annex VI of CLP.

1.7 Current self-classification and labelling

The self-classifications that have been notified are given in the confidential Appendix I (separate file).

2 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

DMTC has CMR property, i.e. reproductive toxicity that justifies a harmonised classification and labelling.

In this aim, a classification proposal was submitted and discussed at ECB (TC C&L) for health endpoints in October 2006.

In this context, all relevant information was collected for health endpoints. Available data indicate that classifications for acute oral and dermal toxicity, acute toxicity by inhalation, skin corrosion and repeated toxicity are also justified as recommended by TC C&L.

It is noted that in the self classification notified by manufacturers and importers, the classifications for these endpoints differs between notifiers and with the proposed harmonized classification:

- For oral acute toxicity, some notifiers apply a classification in category 4
- For dermal acute toxicity, some notifiers apply a classification in category 4
- For acute toxicity by inhalation, some notifiers apply a classification in category 3
- For skin corrosion, some notifiers apply irritant classifications
- For repeated toxicity, some notifiers apply no classification
- For reproductive toxicity, some notifiers apply no classification.

Considering the recommendations of TC C&L and the absence of consensus between notifiers, harmonization of classification on this handover CLH dossier is considered to be required for the different endpoints concluded by the TC C&L.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

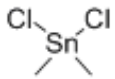
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 5: Substance identity

EC number:	212-039-2
EC name:	-
CAS number (EC inventory):	753-73-1
CAS number:	753-73-1
CAS name:	Stannane, dichlorodimethyl-
IUPAC name:	Dichloro(dimethyl)stannane
CLP Annex VI Index number:	-
Molecular formula:	$C_2H_6Cl_2Sn$
Molecular weight range:	219.67 g/mol

Structural formula:



1.2 Composition of the substance

Table 6: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
DMTC	-		

Table 7: Impurities (non-confidential information)

Impurity	**Typical concentration**	**Concentration range**	**Remarks**
Dimethyltin dichloride is intentionally manufactured as a mixture with monomethyltin trichloride (CAS 993-16-8).			
di/monomethyltin mixtures		approximately 50-99% (by weight);	
Water	-	Ca. 50% w/w;	
Trimethyltin chloride	-	Not defined	
Tin tetrachloride	-	Not defined	

Table 8: Additives (non-confidential information)

Additive	**Function**	**Typical concentration**	**Concentration range**	**Remarks**
No data concerning the additive of Dimethyltin dichloride (CAS 753-73-1) are available.	-	-	-	

1.2.1 Composition of test material

1.3 Physico-chemical properties

Table 9: Summary of physico - chemical properties

Property	**Value**	**Reference**	**Comment (e.g. measured or estimated)**
State of the substance at 20°C and 101,3 kPa	Dimethyltin dichloride may be produced as either an aqueous solution or as a solid material.	Parametrix, Inc. 2000.	Data lacking
Melting/freezing point	90 °C	CRC Handbook of Chemistry and Physics. 1979.	Data lacking
Boiling point	188 - 190 °C at 1013.25 hPa	CRC Handbook of Chemistry and Physics. 1979.	Data lacking
Relative density	1.75 at 25°C	Rohm and Haas Co. 2001.	Data lacking
Vapour pressure	0.26 hPa at 25 °C	USEPA. 2000.	Data lacking
Surface tension	Data lacking	-	-
Water solubility	Conc. at sat. (g/l) 823 g/l at 20°C	Spruit, W.E.T., Schilt, R. 2003 (OECD Guideline 105)	Data lacking
Partition coefficient n-octanol/water	-2.18 at 22 °C	Spruit, W.E.T., Schilt, R. 2003 (OECD Guideline 105)	Measured
Flash point	118°C	CIBA-GEIGY Marienberg GmbH. 1981.	Data lacking
Flammability	Data lacking		
Explosive properties	Data lacking		
Self-ignition temperature	Data lacking		
Oxidising properties	Data lacking		
Granulometry	Data lacking		
Stability in organic solvents and identity of relevant degradation products	Data lacking		
Dissociation constant	Data lacking		
Viscosity	Data lacking		

2 MANUFACTURE AND USES

2.1 Manufacture

Not relevant for this dossier.

2.2 Identified uses

Used as a heat stabilizer in PVC (Parametrix, Inc. 2000).

No use known for general public.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Not evaluated in this dossier.

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Not evaluated in this dossier.

4.2 Acute toxicity

Table 10: Summary table of relevant acute toxicity studies

Method	Results	Remarks	Reference
- **By oral route.** - 5 rats/sex/dose - Test substance: DMTC: MMTC: TMTC; (84.8:15.2:0.5%) **-** Doses: 200, 300 and 500 mg/kg bw	Spontaneous death occurred 2 to 4 days following dosing at 300 mg/kg, and within 24 hours following dosing at 500 mg/kg. LD50 = 409 mg/kg bw		Elf Atochem NA. 1993.
- **By oral route.** - 10 rats/dose - Test substance: DMTC - Doses: 48, 57, 69, 83, 100, 120, and 144 mg/kg bw	LD50 = 73.86 mg/kg bw		Klimmer, O.R. 1971.
- **By oral route.** **-** 6 Rats/dose **-** Test substance: DMTC - Doses : 100, 200, 400, 800, and 1600 mg/kg bw	LD50 = 141.4 mg/kg bw		Affiliated Medical Enterprises, 1971a.
- **By inhalation** - Rats - Test substance: DMTC	- LC_{50} = 0.115 mg/L	OECD 403 compliant	Ciba-Geigy 1977

(purity not known) - Doses: 44, 90, 121, 167 mg/m³ - 4 h exposure to aerosol			
- **By dermal route** - Rabbit - Test substance: DMTC: MMTC; (84.8:15.2%) - Doses: 200, 400 and 750 mg/kg	- LD50 = 404 mg/kg - slight to severe dermal irritation at site of application, urine and fecal staining, diarrhea, decreased food consumption, decreased activity, decreased defecation, tremors, wobbly gait, pale eyes, respiratory abnormalities, mucoid stools, reddened iris, convulsions, dehydration, emaciation, and raised area on the abdominal region.		Rush, R.E. 1993a

4.2.1 Non-human information

4.2.1.1 Acute toxicity: oral

Species	LD50 (mg/kg)	OBSERVATIONS AND REMARKS	Ref.
Rat 5/sex/dose	409 mg/kg bw	Test substance: DMTC: MMTC: TMTC; Purity: 84.8:15.2:0.5%. Doses: 200, 300 and 500 mg/kg bw Clinical abnormalities observed included decreased activity, salivation, rough haircoat, mucoid/soft stools, fecal/urine staining, hunched posture, dehydration, dark material around the facial area, decreased defecation and food consumption, gasping, and rales. Mortality (number of deaths/number tested): 200 mg/kg bw: Males, 0/5; Females 0/5 300 mg/kg bw: Males, 1/5; Females, 3/5 500 mg/kg bw: Males, 2/5; Females, 4/5 Spontaneous death occurred 2 to 4 days following dosing at 300 mg/kg and within 24 hours following dosing at 500 mg/kg. Gross internal findings observed in animals that died included dark red medulla of the kidney, dark red foci on the thymus, mottled lungs, abnormal colored mucoid/fluid contents and eroded area(s), reddened mucosa, and dark red linear striations on	Elf Atochem NA.1993.

		the stomach.	
Rat 10/dose	73.86 mg/kg bw	Test substance: DMTC (purity not known) Doses: 48, 57, 69, 83, 100, 120, and 144 mg/kg bw MORTALITY (number of deaths/total animals/dose group): 48 mg/kg: 1/10 57 mg/kg: 2/10 69 mg/kg: 5/10 83 mg/kg: 6/10 100 mg/kg: 8/10 120 mg/kg: 8/10 144 mg/kg: 10/10 Within 2-3 hours of dosing, animals showed signs of systemic toxicity including lassitude, hypokinesia, lack of appetite, thirst, unkempt fur, general weakness, a tendency to lay on their sides, and death within 24-72 hours of treatment. Recovery of survival animals occurred 4-6 days following the termination of treatment.	Klimmer, O.R. 1971.
Rat 6/dose	141.4 mg/kg bw	Test substance: DMTC (purity not known) Doses : 100, 200, 400, 800, and 1600 mg/kg bw MORTALITY (number of deaths/animals tested; cumulative, Days 7-28): 100 mg/kg: 1/6 (time of death not reported) 200 mg/kg: 5/6 (1 at 8-24 h, 2 at 48 h, 1 at 72 h, 1 at Day 21) 400 mg/kg: 6/6 (4 at 8-24 h, 2 at 72 h) 800 mg/kg: 6/6 (5 at 8-24 h, 1 at 96 h) 1600 mg/kg: 6/6 (6 at 8-24 h) Signs of systemic toxicity observed included depression, convulsions, and death.	Affiliated Medical Enterprises, 1971a.

4.2.1.2 Acute toxicity: inhalation

Species	LC50 (mg/L)	Observations and Remarks	Ref.
Rat	125000 mg/ m^3 125 mg/L	Test substance: DMTC (purity not known) Similar to OECD 403 with shortened duration of exposure Doses: 50, 100, 200, and 300 mg/l 1 h exposure to aerosol Rats exposed to the low dose experienced CNS depression. Gross findings at necropsy included blood in the lungs, heart failure, fluid in the chest cavity, dark spleen, and stomach filled with gas. Calculated LC_{50} on 4 hour using Haber laws and n=1 as recommended in IR/CSA R7.4.4.1 for extrapolation to longer durations: LC_{50}= 31.25 mg/L	Wells Laboratories, 1975.
Rat	1632 mg/m^3 1.6 mg/L	Test substance: DMTC (purity not known) Similar to OECD 403 with shorter duration of exposure Doses: 640, 1679, and 3012 mg/m³ 1 h exposure to aerosol Calculated LC_{50} on 4 hour using Haber laws and n=1 as recommended in IR/CSA R7.4.4.1 for extrapolation to longer durations: LC_{50}= 0.4 mg/L	Ciba-Geigy, 1977
Rat	115 mg/m^3 0.115 mg/L	Test substance: DMTC (purity not known) OECD 403 compliant Doses: 44, 90, 121, 167 mg/m³ 4 h exposure to aerosol	Ciba-Geigy 1977
Rat	>5.77 mg/l	Test substance: DMTC (purity not known) Similar to OECD 403 with shorter duration of exposure Doses: 5.00 and 5.77 mg/l 1 h exposure to aerosol No deaths observed Calculated LC_{50} on 4 hour using Haber laws and n=1 as recommended in IR/CSA R7.4.4.1 for extrapolation to longer durations: LC_{50}>1.44 mg/L	Hazelton Laboratories 1976
Rat	>56.7 mg/l	Test substance: DMTC (purity not known) Similar to OECD 403 with shorter duration of exposure	International Bio-Research

		1 h exposure to vapor No deaths observed Calculated LC_{50} on 4 hour using Haber laws and n=1 as recommended in IR/CSA R7.4.4.1 for extrapolation to longer durations: LC_{50}> 14.2 mg/L	1976
Rat	>16.7 mg/l	Test substance: DMTC Similar to OECD 403 with shorter duration. 1 h exposure to vapor No deaths observed Calculated LC_{50} on 4 hour using Haber laws and n=1 as recommended in IR/CSA R7.4.4.1 for extrapolation to longer durations: LC_{50}> 4.2 mg/L	International Bio-Research 1976

4.2.1.3 Acute toxicity: dermal

Species	LD50 (mg/kg)	Observations and Remarks	Ref.
Rabbit	> 2000	Test substance: DMTC: MMTC; (90:10%) Performed as a limit test. No mortality.	Affiliated Medical Enterprises 1971b
Rabbit	404	Test substance: DMTC: MMTC; (84.8:15.2%) Doses: 200, 400 and 750 mg/kg Mortality (number of dead/total number of animals tested), by sex and dose: 200 mg/kg: 0/5 males, 0/5 females 400 mg/kg: 4/5 males, 2/5 females 750 mg/kg: 4/5 males, 5/5 females Clinical abnormalities reported included slight to severe dermal irritation at site of application, urine and fecal staining, diarrhea, decreased food consumption, decreased activity, decreased defecation, tremors, wobbly gait, pale eyes, respiratory abnormalities, mucoid stools, reddened iris, convulsions, dehydration, emaciation, and raised area on the abdominal region.	Rush, R.E. 1993b

4.2.1.4 Acute toxicity: other routes

Not evaluated in this dossier.

4.2.2 Human information

No data available.

4.2.3 Summary and discussion of acute toxicity

In the oral acute toxicity on DMTC at 84.8% in mixture with MMTC (Elf Atochem NA.1993), spontaneous death occurred 2 to 4 days following dosing at 300 mg/kg, and within 24 hours following dosing at 500 mg/kg and the LD_{50} was determined at 409 mg/kg bw. It is noted that MMTC at 90% in mixture with DMTC has a LD_{50} of 1158 mg/kg (Elf Atochem 1993) and DMTC is considered more toxic than MMTC. The presence of MMTC therefore does not explain the acute toxicity obtained on DMTC at 84.8%.

Two studies are available on DMTC only although purity is not known. In the study of Klimmer (1971), animals showed signs of systemic toxicity within 2-3 hours of dosing and death within 24-72 hours of treatment. The LD_{50} was determined at 73.86 mg/kg bw. In the study of "Affiliated Medical Enterprises" (1971a), signs of systemic toxicity were observed, included depression, convulsions, and death. The LD_{50} was determined at 141.4 mg/kg bw.
By **inhalation** a number of studies with exposure to both aerosol and vapor at 1 and 4 hours were reported with DMTC of unknown purity. From studies performed on a 1h exposure, calculated 4-hour LC_{50} values range from 0.4 to >1.44 mg/L for aerosols and exceed 4.2 to 14.2 mg/L for vapours. A single study was performed with a 4h exposure and was considered more reliable as it is consistent with OCDE guidelines. In this study, an LC_{50} value of 0.115 mg/L was reported for a 4 hours aerosol exposure.

In a **dermal** study on DMTC at 84.8% in mixture with MMTC (Rush, R.E. 1993b), there were no deaths at 200 mg/kg, 4/5 males and 2/5 females died at 400 mg/kg and 4/5 males and 5/5 females died at 750 mg/kg. A variety of clinical abnormalities were observed including slight to severe dermal irritation at the site of application. This resulted in an **LD_{50} value of 404 mg/kg.** DMTC is considered more toxic than MMTC. The presence of MMTC therefore does not explain the low LD_{50} value obtained on DMTC at 84.8%.

4.2.4 Comparison with criteria

The lowest acute oral LD_{50} values for DMTC are between 50 and 300 mg/kg bw and a classification "**Acute Tox. 3, H301**" is proposed according to **CLP.**

The lowest acute oral LD_{50} values for DMTC are between 25 and 200 mg/kg bw and support a classification "**T; R25"** according to Directive **67/548/EEC.**

The acute LC_{50} value by inhalation route for DMTC is between 0.05 and 0.5 mg/L 0.5 mg/L further to aerosol exposure for 4 hours and a classification "**Acute Tox. 2, H330**" is proposed according to **CLP.**

The acute LC_{50} value by inhalation route for DMTC is less than 0.25 mg/L further to aerosol exposure for 4 hours and support a classification "**T^+; R26"** according to Directive **67/548/EEC.**

The lowest acute dermal LD_{50} value for DMTC is between 200 and 1000 mg/kg bw and a classification "**Acute Tox. 3, H311**" is proposed according to **CLP.**

The lowest acute dermal LD_{50} value for DMTC is between 400 and 2000 mg/kg bw and support a classification **"T; R24"** according to Directive **67/548/EEC.**

4.2.5 Conclusions on classification and labelling of acute toxicity

For the **acute oral toxicity** a classification "**Acute Tox.3; H301**" is proposed (**T; R25** according to the Directive 67/548/EEC).

For the acute toxicity by inhalation, a classification "**Acute Tox.2; H330**" is proposed (**T^+ R26** according to the Directive 67/548/EEC).

For the dermal acute toxicity, a classification "**Acute Tox. 3; H311**" is proposed (**T; R24** according to the Directive 67/548/EEC).

RAC evaluation of Acute toxicity

Summary of Dossier submitter's proposal
The CLH report includes three oral acute toxicity studies in rats. Two were conducted with DMTC alone of an unknown purity and one with 84.8% DMTC in a mixture with monomethyltin chloride (MMTC, 15.2%) and trimethyltin trichloride (TMTC, 0.5%). The lowest reported oral LD_{50} was 73.86 mg/kg and the dossier submitter proposed a CLP classification of Acute Tox. 3 – H301(DSD: T; R25).
Six inhalation toxicity studies in rats are reported in the CLH report using DMTC in either vapour or aerosol form. One study is reported as OECD Test Guideline (TG) 403-compliant with an LC_{50} value of 0.115 mg/L (4h exposure to aerosol). Other studies used exposures of a shorter duration (1h) and are included as supportive information. The DS proposed a CLP classification of Acute Tox. 2 – H330 ((DSD: T+; R26).
One OECD TG 404 compliant dermal acute toxicity and one range finding study in rabbits are reported, both using a mixture of DMTC and MMTC (84.5%:15.2% and 90%:10%, respectively). The lowest reported LD_{50} was 404 mg/kg bw/day and the DS proposed a CLP classification of Acute Tox. 3 – H311 (DSD: Xn; R21).

Comments received during public consultation
Three comments were received during public consultation. One Member State (MS) agreed with the proposal while another suggested classifying DMTC as T; R24 for dermal acute toxicity as the LD_{50} value observed was only slightly above the guidance value for R24. The DS agreed with the suggestion by the MS and these changes are reflected in a revised version of the CLH report, provided as an appendix to the RCOM.

In addition, one comment was received from industry, providing additional human data on acute toxicity of DMTC. Further details can be found in the RCOM.

RAC assessment and comparison with criteria
An oral acute toxicity study using a mixture of 84.8% DMTC with MMTC resulted in a LD_{50} of 409 mg/kg bw in rats. Since MMTC at 90% in mixture with DMTC has a LD_{50} of 1158 mg/kg in rats, DMTC is considered more toxic than MMTC and the LD_{50} is considered relevant for DMTC (Elf Atochem 1993). Two other oral acute toxicity studies in rats on DMTC revealed an LD_{50} of 73.86 mg/kg bw (Klimmer 1971) and 141.4 mg/kg bw ("Affiliated Medical Enterprises", 1971a). Neither study provides information on impurities. Since the latter two LD_{50} values are between 50 and 300 mg/kg bw RAC agrees with the proposal of the DS that a classification "Acute Tox. 3 - H301" according to CLP is warranted. However the RAC notes that the more recent study using approx.. 85% pure DMTC resulted in a LD_{50} of 409 mg/kg bwt, which is above the limit value for Acute Tox. 3 under CLP.
The lowest acute oral LD_{50} values for DMTC are between 25 and 200 mg/kg bw and RAC agrees with the proposal of the DS that a classification "T; R25"

according to DSD is warranted.

Acute inhalation studies with exposure to DMTC aerosol and vapour of unknown purity for 1 and 4 hours have been performed in rats. For DMTC as an aerosol, the only study using a 4-hour exposure resulted in a LC_{50} of 0.115 mg/L. The other LC_{50} values are based on 1-hour exposures, which have been extrapolated to 4 hours according to Haber's law. The resulting 4-hour LC_{50} values are 0.4, > 1.44, and 31.25 mg/L. The LC_{50} values of 0.115 and 0.4 mg/L would result in acute toxicity category 2, the value of 1.44 in category 4, and for the highest LC_{50} value no classification would be warranted. Since the study resulting in the lowest LC_{50} value of 0.115 is consistent with OECD TG 403, this value has been used for classification and acute toxicity category 2 has been proposed. The reliability of the three studies with the higher LC_{50} values was not evaluated because the full study reports were not available to the RAC. RAC notes that for DMTC vapours 4-hour LC_{50} of > 4.2 and > 14.2 mg/L have been determined, without deaths in either of these studies.
Based on the aerosol studies, RAC agrees with the DS that classification as Acute Tox. 2,- H330 according to CLP is warranted.

The acute LC_{50} value by the inhalation route for DMTC is less than 0.25 mg/L following aerosol exposure for 4 hours. RAC supports the DS in a DSD classification proposal of "T+; R26" .

In a dermal acute study in rabbits using DMTC at 84.8% in a mixture with MMTC (Rush 1993a), there were no deaths at 200 mg/kg; 4/5 males and 2/5 females died at 400 mg/kg and 4/5 males and 5/5 females died at 750 mg/kg, from which a LD_{50} value of 404 mg/kg has been determined. Since the resulting LD_{50} is between 200 and 1000 mg/kg bwt, RAC agrees with the DS proposal that a classification "Acute Tox. 3, H311" according to CLP is warranted.

A previous study by Affiliated Medical Enterprises (1971b) resulting in an LD_{50} of > 2000 mg/kg has been insufficiently documented and has not been considered relevant for classification. As the lowest acute dermal LD_{50} value for DMTC is only just above the cut-off value of 400 mg/kg bw for classification with "T; R24" according to DSD and 6/10 animals died at 400 mg/kg bw, RAC supports a classification with "T; R24" as suggested during public consultation and subsequently agreed by the DS.

4.3 Specific target organ toxicity – single exposure (STOT SE)

Not evaluated in this dossier.

4.4 Irritation

Not evaluated in this dossier.

4.5 Corrosivity

4.5.1 Skin corrosivity

Species	No. of animals	Exp. time	Conc. (wt/	Dressing	Observations and remarks (specify the experimental conditions, score and evaluation method)	Ref.

			wt)			
Rabbit (albino New Zealand strain)	6 males	**One period of exposure:** 24 h **Two observation periods:** 24 h and 72 h	0.5 g Undiluted	Occlusive	Test substance: DMTC (purity not known) Method used: Draize test: Experimental procedure: The skin on the dorsal surface of the rabbits was shaved free of hair by means of electric clippers. Twelve dorsal test areas were utilized; half of the dorsal test areas were abraded down to, but not through the dermis, using a hypodermic needle. The remaining test areas were left intact. Standard patch test plasters (1"*1" gauze pad) were saturated with 0.5 g of DMTC and applied to the dermal test area. The patch test plasters were left in place for **24 hours (period of exposure)**. The test areas were scored for dermal irritation immediately following the **24 hours exposure period (observation period)** and again at **72 hours (other observation period)**, according to the method of Draize. Effects observed included moderate to severe erythema and eschar formation on all animals, at both intact and abraded skin sites, at 24 and 72 hours. Very slight oedema was observed on all animals at both sites at 24 hours. No oedema was observed at 72 hours. PDII (Primary Dermal Irritation Index) 1.75	Affiliated Medical EnterprisesInc.1971c.
Rabbit (New Zealand white rabbits)	3/sex	**One period of exposure:** 4 h **observation periods:** at 1 h, 24 h, 48 h and 72 h after patch removal	0.5 ml as a 50% solution	Semi-occlusive	Test substance: DMTC: MMTC; (84.8:15.2%) Method used: Test guideline 404 of the OECD Experimental procedure: On the day prior to dosing, the fur was clipped from the dorsal area of the trunk of each animal without accidental abrasion to the skin. On the day of dosing, 0.5 ml of DMTC was applied to a small area of intact skin on each animal (1 inch * 1 inch) and covered with a gauze patch. After a four-hour exposure period, the gauze patch was removed from each animal. Residual test substance was removed where practical using gauze moistened with distilled water.	Rush, R.E. 1993b.

					Animal were examined for signs of erythema and oedema and the responses scored at approximately 1, 24, 48, and 72 hours after patch removal according to the Dermal Irritation Grading system. Analyses of data: No mortality. Exposure to the test substance produced **blanching** and **necrosis** with **severe oedema** on 6/6 sites within **1 hour** after patch removal. Dermal irritation progressed to **eschar** on 3/6 sites by study termination (**72-h**).	

4.5.2 Summary and discussion

In the AME study (1971c), very slight oedema was observed on all animals at both intact and abraded skin sites at 24 hours. No oedema was observed at 72 hours. The Primary Dermal Irritation Index is evaluated at 1.75. Moderate to severe erythema and eschar formation were observed on all animals, at both skin sites, at 24 and 72 hours. So according to the evaluation of Draize, the substance would be considered a moderate irritant to the skin.

In the Rush study (1993b), blanching and necrosis with severe oedema were observed on all dermal sites within 1 hour after a four-hour exposure time, with irritation progressing to eschar in 3 sites by termination (72 hours). Under the conditions of the test, the substance would be considered to be corrosive to rabbit dermal tissue.

4.5.3 Comparison with criteria

Criteria of classification based on animal data according to 67/548/EEC and CLP regulations are similar and refer to cases where there are positive results from appropriate animal tests. In particular, the classification in corrosive category 1 and subcategories depends on two factors: the period of exposure and the period of observation of the positive effects (erythema, oedema, eschar...).

In the AME (1971c) study, the exposure period of 24 hours is too long for a classification of DMTC in the skin corrosive category. Thus, this study does not allow the classification of the substance in the skin corrosive category.

In the second study (Rush, R.E. 1993b), a positive result was obtained after a four-hour of application on the rabbit dermal tissue with an observation period from 1 hour to 72 hours, so the test substance was considered to be corrosive. As positive results are observed in the observation period of 1 hour after the four-hour exposure, the substance can be classified in category 1C of skin corrosive.

4.5.4 Conclusions on classification and labelling

For the skin corrosion, a classification **Skin Corr.1C H314** is proposed according to the CLP regulation (**C; R34** according to the directive 67/548/EEC).

Based on this classification, it is appropriated to adopt EUH071-Corrosive to the respiratory tract.

RAC evaluation of Irritation/Corrosion

Summary of Dossier submitter's proposal
The DS includes two studies on skin irritation/corrosion in the CLH report. One Draize test study, conducted in rabbits with DMTC alone (Affiliated Medical Enterprises, 1971c) showed moderate irritation and one OECD TG 404 compliant study in rabbits, conducted with a mixture of DMTC and MMTC (84.8%:15.2%) (Rush 1993b) reported corrosive effects on rabbit skin. The DS proposed classification as Skin Corr. 1B – H314 according to CLP and C; R34 according to DSD.

Comments received during public consultation
Comments were received from two MS during public consultation. One MS suggested that the dataset does not allow for differentiation into subcategories and supported classification as Skin Corr. 1 – H314. It also suggested the addition of hazard statement EUH071 – Corrosive to the respiratory tract. Another MS asked for further clarification on the appearance of the response. The DS agreed that classification in the subcategory 1B is not appropriate and proposed category 1C instead, along with the addition of EUH071. These changes are reflected in a revised version of the CLH report, supplied as an appendix to the RCOM. Further details are available in the RCOM

RAC assessment and comparison with criteria
In the Affiliated Medical Enterprises study (1971c), very slight oedema was observed on all animals at both intact and abraded skin sites at 24 hours. No oedema was observed at 72 hours. The Primary Dermal Irritation Index is evaluated at 1.75. Moderate to severe erythema and eschar formation were observed on all animals, at both skin sites, at 24 and 72 hours. According to the evaluation criteria of the Draize test, the substance would be considered a moderate irritant to the skin.

In the Rush (1993b) study, blanching and necrosis with severe oedema were observed on all dermal sites within 1 hour after a four-hour exposure time, with irritation progressing to eschar in 3 sites by termination of the observation period (at 72 hours). Under the conditions of the test, the substance would be considered to be corrosive to rabbit dermal tissue.

In the Affiliated Medical Enterprises (1971c) study, the exposure period of 24 hours is too long for the data to be used for classification of DMTC for skin corrosion. Thus, RAC concluded that this study does not allow the classification of the substance in the skin corrosive category.

In the second study (Rush, 1993b), a positive result was obtained after a four-hour application on the rabbit dermal tissue with an observation period from about 1 hour to 72 hours, so the test substance was considered to be corrosive. As positive results were noted during the observation period of 1 hour after the four-hour exposure, classification in category 1C for skin corrosion has been proposed.
However, the RAC noted that neither study provides sufficient information on whether corrosive effects occur after a shorter exposure (i.e., ≤ 3 min for subcategory 1A, or between 3 min and 1 hr for subcategory 1B) so that no differentiation between the subcategories can be made, in contrast to the original proposal by the DS.

For skin corrosion, RAC agreed that a classification **Skin Corr.1 H314** according to CLP regulation (DSD: **C; R34**) is warranted.

As DMTC is acutely toxic via inhalation and corrosive to skin, RAC additionally concluded that it is appropriate to add EUH071 (corrosive to the respiratory tract).

4.6 Sensitisation

Not evaluated in this dossier.

4.7 Repeated dose toxicity

4.7.1 Non-human information

4.7.1.1 Repeated dose toxicity: oral

Table 11: Summary table of relevant repeated dose toxicity studies

Method	Results	Remarks	Reference
Repeated dose toxicity study -during 13 weeks -on 15 rats/sex/dose. -3 doses: 25, 75, and 200 ppm -oral route, in drinking water	In the 200 ppm group: in the 5 first weeks, 21 females and 7 males died or were sacrificed, numerous clinical signs of toxicity were observed. In the 75 ppm group: one male died, body weights were reduced, and neuropathological lesions were observed. In the 25 ppm group: food (males only) and water intake and neuropathological lesions. NOAEL < 25 ppm.	Reproductive organs have not been evaluated in this study.	Rohm and Haas Co. 1999.
Repeated dose toxicity study -during 13 weeks -on 10 rats/sex/dose -4 doses: 1, 6, 15, and 200 ppm -oral route, in diet	Deaths, severe neurological and neurobehavioural signs were observed at 200 ppm. Microscopic examination was not performed in lower dose animals. NOAEL = 15 ppm	Reproductive organs have not been evaluated in this study.	Elf Atochem NA. 1996.

Species	Dose, ppm in the drinking water or in the diet (mg/kg body weight)	Duration of treatment	Observations and Remarks	Ref.
Sprague-Dawley Rats	25, 75, and 200 ppm	13 weeks (90 days)	**Test substance:** Dimethyltin Dichloride: Methyltin Trichloride (90:10% mixture), Similar to OECD Guideline 408 (Repeated dose 90-Day	Rohm and

(15/sex/dose for the main study and 15/sex/dose for the neurotoxicity component)	By oral route, in drinking water(equivalent to 1.6, 5.2 and 15.50 mg/kg bw/day in males and 2.2, 6.7 and 19.5 mg/kg bw/day in females)		oral toxicity in rodents) and 424 (Neurotoxicity in rodents). **<u>General toxicity:</u>** **200 ppm (15.50 mg/kg bw/day in males; 19.5 mg/kg bw/day in females):** During the first 5 weeks, 7 males and 21 females in the 200 ppm group (15.50 mg/kg bw/day in males; 19.5 mg/kg bw/day in females) died or were sacrificed, due to poor condition. All remaining animals were sacrificed by Week 6. Animals in the 200 ppm group (15.50 mg/kg bw/day in males; 19.5 mg/kg bw/day in females) showed clinical signs of toxicity, including tremors, convulsions and aggression/ hypersensitivity/ difficulty when handled. Animals appeared to be weak, thin, and dehydrated, were cold to touch, were observed lying on their sides, and had decreased home-cage activity levels. An increased incidence of fur staining was also noted. Body weights and food intake were significantly lower for the 200 ppm group (15.50 mg/kg bw/day in males; 19.5 mg/kg bw/day in females) at all intervals. **75 ppm (5.2 mg/kg bw/day in males; 6.7 mg/kg bw/day in females):** One male was found dead during Week 6 (no other deaths occurred). Abnormal clinical signs were limited to tremors, hypersensitivity (difficulty when handled), a thin dehydrated body condition for the male that died, a transitory dehydrated appearance for another male, and hypersensitivity, convulsions, and reduced activity for one female. Body weights and food consumption were significantly lower for males at most intervals measured following treatment. **25 ppm (1.6 mg/kg bw/day in males; 2.2 mg/kg bw/day):** Water consumption significantly decreased for all treated groups during most intervals measured; however, following treatment termination, water consumption values were generally comparable between the treated groups and the control. Functional Observational Battery (FOB) tests indicated several findings, primarily affecting the 200 ppm group (15.50 mg/kg bw/day in males; 19.5 mg/kg bw/day in females). At Week 4, females showed significantly reduced rearing, lower hindlimb grip strength, and decreased body temperature. Ataxic gait was observed for one male, along with tremors and clonus of jaws. Three females showed tremors and clonic convulsions. Hunched posture was observed for one male, and for one female ataxia was noted, as well as a red liquid	Haas Co. 1999.

			material at the urogenital region. Significant findings for the 75 ppm group (5.2 mg/kg bw/day in males; 6.7 mg/kg bw/day in females) were limited to lower body temperature of females. One male showed ataxia and unusual hind limb movements (which were also observed for this animal on subsequent testing occasions). At Weeks 8, 13, and following recovery, rearing was significantly decreased for the 75 ppm (6.7 mg/kg bw/day in females) females and their body temperature was significantly decreased at the Week 13 assessment. At Week 13, the rate of linear decrease was significantly lower for the 75 ppm (6.7 mg/kg bw/day in females) females relative to the control group. There were significant blood biochemical changes for males in the 200 ppm group (15.50 mg/kg bw/day in males) at Week 4, which included increases in BUN, creatinine, and phosphorus and decreases in potassium levels. Many of the animals sacrificed by Week 6 showed marked changes in various blood biochemical parameters, including increases in BUN, creatinine, AST, ALT, and phosphorus. Males in the 200 ppm group (15.50 mg/kg bw/day in males) had an elevated urine pH at Week 4. Absolute and relative thymus weights were significantly decreased for the 200 ppm (15.50 mg/kg bw/day in males) males at the interim sacrifice (Week 4) and 75 ppm males (5.2 mg/kg bw/day in males) at termination sacrifice. Absolute heart weight was decreased significantly for 25 and 75 ppm (2.2 mg/kg bw/day and 6.7 mg/kg bw/day in females, respectively) females at interim sacrifice, but not at terminal sacrifice. Absolute and relative kidney weights were significantly increased for 25 ppm and 75 ppm (2.2 mg/kg bw/day and 6.7 mg/kg bw/day in females, respectively) females at terminal sacrifice. Gross pathological findings for preterminal animals included small thymus and/or spleen, emaciated carcass, dilation of digestive tract/discolored digestive material, and dark areas on the stomach and/or lungs. A small thymus was also seen at the interim evaluation for 200 ppm males (15.50 mg/kg bw/day in males) and at the terminal evaluation for the 75 ppm group (5.2 mg/kg bw/day in males; 6.7 mg/kg bw/day in females). Results of the histopathological examinations indicated clear treatment related nervous system lesions for preterminal 200 ppm (15.50 mg/kg bw/day in males; 19.5 mg/kg bw/day in females) animals in various	

			regions of the brain and spinal cord, characterized by slight to mild ventricular dilation, mild to moderate neuronal necrosis, and slight to mild white matter vacuolization. Nervous system changes were observed for 75 ppm (5.2 mg/kg bw/day in males; 6.7 mg/kg bw/day in females) animals at terminal examination (although slight and less frequent) and possible treatment-related lymphoid atrophy was observed for this group. Animals in the 25 ppm group (1.6 mg/kg bw/day in males; 2.2 mg/kg bw/day) showed slight to moderate vacuolization in brain and spinal cord tissue at the terminal examination. Overall, treatment of male and female rats with a 90:10% mixture of dimethyltin: monomethyltin chloride (administered in drinking water) resulted in death, reduced body weight, decreased food and water intake, blood biochemical changes, behavioral effects, and neuropathological lesions at 200 ppm (equivalent to 15.5 and 19.5 mg/kg/day for males and females, respectively). At 75 ppm (equivalent to 5.2 and 6.7 mg/kg/day for males and females, respectively), one male died, body weights were reduced (males only), food and water intake were decreased, motor activity was reduced (females only), and neuropathological lesions were observed. For the 25 ppm group (equivalent to 1.6 and 2.2 mg/kg/day for males and females, respectively), no mortality occurred and treatment-related findings were limited to reduced food (males only) and water intake and neuropathological lesions. The no-observed-adverse-effect level (**NOAEL**) was considered to be **less than 25 ppm.**	
Wistar Rats 10/sex/dose	1, 6, 15, and 200 ppm or mg/kg diet By oral route in diet. (equivalent to 0.06, 0.39, 0.98 and 16.81 mg/kg bw/day in males and 0.07, 0.41,	13 weeks (90 days)	**<u>Test substance:</u>** Dimethyltin Dichloride: Methyltin Trichloride (66.5:33.5% mixture). Similar to OECD Guideline 408 (Repeated dose 90-Day oral toxicity in rodents) **<u>General toxicity:</u>** Three females of the 200 ppm group (17.31 mg/kg bw/day in females) died during the first month and most males, and remaining females in this group showed severe neurological and neurobehavioural signs, including tremors, convulsions, and increased footsplay. All remaining animals of the 200 ppm group (16.81 mg/kg bw/day in males; 17.31 mg/kg bw/day in females) were sacrificed.	Elf Atochem NA., 1996.

	1.02 and 17.31 mg/kg bw/day in females)		Mean body weight for males of the 200 ppm group (16.81 mg/kg bw/day in males) on Days 7 and 28 were significantly lower. Food consumption on Day 7 was significantly decreased in animals (both sexes) of the 200 ppm group (16.81 mg/kg bw/day in males; 17.31 mg/kg bw/day in females) and increased in females on Day 28. Food conversion efficiency was significant only for high-dose males on Day 21. Mean water consumption was significantly reduced in females (6 ppm group [0.41 mg/kg bw/day in females]) on Day 6 only. Mean intake of the test substance in animals receiving 1, 6, 15, or 200 mg/kg diet (0.06, 0.39, 0.98 and 16.81 mg/kg bw/day in males and 0.07, 0.41, 1.02 and 17.31 mg/kg bw/day in females, respectively) were 0.06, 0.39, 0.98, and 16.81 mg/kg bw/day in males and 0.07, 0.41, 1.02, and 17.31 mg/kg bw/day in females. There was a significant increase in alanine aminotransferase and aspartate aminotransferase in males of the 1 ppm group (0.06 mg/kg bw/day in males). The specific gravity of urine was significantly increased in females of the 6 ppm dose group (0.41 mg/kg bw/day in females). Upon microscopic examination, treatment-related histopathological changes were observed in the brain, the kidneys, and the thymus of animals treated with 200 ppm (16.81 mg/kg bw/day in males; 17.31 mg/kg bw/day in females) of the test substance. Macroscopic pathological observations showed some gross skin changes that were probably treatment-related (200 ppm [16.81 mg/kg bw/day in males; 17.31 mg/kg bw/day in females]). Animals in the lower dose groups were not examined microscopically. Neuropathological examinations showed that animals in the high dose group (200 ppm [16.81 mg/kg bw/day in males; 17.31 mg/kg bw/day in females]) showed signs of convulsions, tremors, blepharospasm, and hunched posture. Microscopic observations showed pronounced neuronal death in a number of areas of the cerebellum in the 200 ppm group (16.81 mg/kg bw/day in males; 17.31 mg/kg bw/day in females) (more pronounced in females). The areas with predominant lesions were the hippocampal region, the piriform, entorhinal, and perirhinal cortices, the amygdala, the olfactory nuclei and the tenia tecta. A slight increase in swollen axons in the spinal cord was observed in the 200 ppm group (16.81 mg/kg bw/day in males; 17.31 mg/kg bw/day in females). Based on the effects described above, particularly the	

			neurotoxic effects observed in the high dose group, the **NOAEL** was placed at **15 ppm**. This was equivalent to **0.98 mg/kg bw/day (males)** and **1.02 mg/kg bw/day (females)** of the test mixture or **0.62** mg/kg bw/day (males) and **0.65** mg/kg bw/day (females) for the **dimethyltin dichloride component** of the mixture. The overall NOAEL for neuropathology is considered to be 0.6 mg/kg body weight for the dimethyltin dichloride component of the mixture (Elf Atochem, feeding study). Marginal effects were seen at 1.4 and 2 mg/kg body weight for males and females respectively, in the drinking water study (Rohm and Haas) and clear effects at 4.6 and 6 mg/kg bw for males and females respectively in the drinking water study (Rohm and Haas).	

4.7.1.2 Repeated dose toxicity: inhalation

Not evaluated in this dossier.

4.7.1.3 Repeated dose toxicity: dermal

Not evaluated in this dossier.

4.7.1.4 Repeated dose toxicity: other routes

Not evaluated in this dossier.

4.7.1.5 Human information

No data

4.7.1.6 Summary and discussion of repeated dose toxicity

Together, these two oral 90-day studies on DMTC indicate that the main target organ is the nervous system. Deaths and severe neurological signs occurred from 75 ppm (5.2/6.7 mg/kg) in Rohm and Haas 1999 and at 200 ppm (16.81/17.31 mg/kg) in Elf Atochem 1996. Besides, neuropathological lesions were observed from the lowest dose of 25 ppm (1.6/2.2 mg/kg) in Rohm and Haas 1999 as evidenced by moderate vacuolization in the brain and spinal cord tissue and ventricular dilation and neuronal necrosis at highest doses. Similar lesions were found at 200 ppm (16.81/17.31 mg/kg) in Elf Atochem 1996 but histopathology was not performed at lower doses.

4.7.1.7 Summary and discussion of repeated dose toxicity findings relevant for classification according to DSD

Under DSD, the following effects are considered as serious damage:

(a) substance-related deaths;

(b) (i) major functional changes in the central or peripheral nervous systems, including sight, hearing and the sense of smell, assessed by clinical observations or other appropriate methods (e.g. electrophysiology);

(ii) major functional changes in other organ systems (for example the lung);

(c) any consistent changes in clinical biochemistry, haematology or urinalysis parameters which indicate severe organ dysfunction. Haematological disturbances are considered to be particularly important if the evidence suggests that they are due to decreased bone marrow production of blood cells;

(d) severe organ damage noted on microscopic examination following autopsy:

(i) widespread or severe necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity (e.g. liver);

(ii) severe morphological changes that are potentially reversible but are clear evidence of marked organ dysfunction (e.g. severe fatty change in the liver, severe acute tubular nephrosis in the kidney, ulcerative gastritis); or

(iii) evidence of appreciable cell death in vital organs incapable of regeneration (e.g. fibrosis of the myocardium or dying back of a nerve) or in stem cell populations (e.g. aplasia or hypoplasia of the bone marrow).

In the available 90-day studies study DMTC induced:

- Deaths from 75 ppm (5.2/6.7 mg/kg) in the drinking water study (Rohm and Haas, 1999) relevant for criteria (a)
- Histopathological lesions in the brain from 25 ppm (1.6/2.2 mg/kg) in the drinking water study (Rohm and Haas, 1999) relevant for criteria (d) (ii)
- The main effects target the nervous system.

4.7.1.8 Comparison with criteria of repeated dose toxicity findings relevant for classification according to DSD

By oral route, substances shall be classified as toxic under DSD when they cause serious damage at levels of order ≤ 50 mg/kg in a 90-day study.

Both critical effects identified above in the 90-day studies occur below the threshold of 50 mg/kg.

4.7.1.9 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification according to DSD

A classification T; R48/25 is proposed according to the Directive 67/548/EEC.

4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

4.8.1 Summary and discussion of repeated dose toxicity findings relevant for classification as STOT RE according to CLP Regulation

Under CLP, the following effects are considered as relevant:

(a) morbidity or death resulting from repeated or long-term exposure. Morbidity or death may result from repeated exposure, even to relatively low doses/concentrations, due to bioaccumulation of the substance or its metabolites, and/or due to the overwhelming of the de-toxification process by repeated exposure to the substance or its metabolites;

(b) significant functional changes in the central or peripheral nervous systems or other organ systems, including signs of central nervous system depression and effects on special senses (e.g. sight, hearing and sense of smell);

(c) any consistent and significant adverse change in clinical biochemistry, haematology, or urinalysis parameters;

(d) significant organ damage noted at necropsy and/or subsequently seen or confirmed at microscopic examination;

(e) multi-focal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity;

(f) morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction (e.g., severe fatty change in the liver);

(g) evidence of appreciable cell death (including cell degeneration and reduced cell number) in vital organs incapable of regeneration.

In the available 90-day studies study DMTC induced:

- Deaths from 75 ppm (5.2/6.7 mg/kg) in the drinking water study (Rohm and Haas, 1999) relevant for criteria (a)
- Histopathological lesions in the brain from 25 ppm (1.6/2.2 mg/kg) in the drinking water study (Rohm and Haas, 1999) relevant for criteria (d) and (f)
- The main effects target the nervous system.

4.8.2 Comparison with criteria of repeated dose toxicity findings relevant for classification as STOT RE

By oral route, substances shall be classified under CLP in category 1 when they cause significant and/or severe toxic effects of relevance to human health at levels of order ≤ 10 mg/kg in a 90-day study.

Both critical effects identified above in the 90-day studies occur below the threshold of 10 mg/kg.

4.8.3 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification as STOT RE

A classification **STOT RE 1- H372** is proposed according to the CLP.

The main target organ identified is the central nervous system and it is proposed to add **nervous system** to the hazard statement.

A SCL is allocated if the effective dose level or concentration is 10 times below the guidance values according to the CLP, that corresponds to an effective dose below 1 mg/kg bw. So no SCL is determined for DMTC according to the CLP regulation.

RAC evaluation of Specific target organ toxicity/Repeated dose toxicity

Summary of Dossier submitter's proposal

Two repeated dose toxicity studies on DMTC are presented in the CLH report, one 90-day oral (drinking water) repeated dose study in rats similar to OECD TG 408 and OECD TG 424 (neurotoxicity in rodents) (Rohm and Haas, 1999) and one 90-day oral (diet) repeated dose study in rats similar to OECD TG 408 (Elf Atochem, 1996). The DS proposed classification as STOT RE 1 according to CLP and T; R48/25 according to DSD with the nervous system as the main target organ.

Comments received during public consultation

One MS supported the proposal during public consultation but asked that further consideration be given to addition of STOT SE 3, based on information from the public C&L inventory. Further details can be found in the RCOM.

RAC assessment and comparison with criteria

In both oral 90-day studies on DMTC the main target organ was the nervous system. Severe neurological signs and deaths occurred from 75 ppm (5.2/6.7 mg/kg) in the Rohm and Haas (1999) study as evidenced in the histopathology by moderate vacuolisation in the brain and spinal cord tissue and ventricular dilation and neuronal necrosis at highest doses. At 25 ppm (equivalent to 1.6 and 2.2 mg/kg/day for males and females, respectively), no mortality occurred and treatment-related findings were limited to reduced food (males only) and water intake and neuropathological lesions with moderate vacuolisation in brain and spinal cord tissue. The NOAEL was considered to be less than 25 ppm. In the Elf Atochem (1996) study, severe neurological signs and deaths occurred at 200 ppm (16.81/17.31 mg/kg for males and females, respectively) with similar lesions like those found in the Rohm and Haas (1999) study. Histopathology was not performed at the lower doses. The overall NOAEL for neuropathology was 0.6 mg/kg bw for the dimethyltin dichloride component of the mixture.

The critical effects (deaths and histopathological lesions in the brain) identified in the 90-day studies occur between 1.6 and 6.7 mg/kg bw/day in both male and female rats.

The RAC notes that absolute and relative weights of the thymus have been reduced in a 90-day oral study, with effect levels at about 5 mg/kg bw in males (Rohm and Haas 1999), and in another 90-day oral study at about 15 mg/kg bw/day in both sexes (including histopathological lesions) (Elf Atochem 1996). Since no histochemical analysis has been performed at the lower dose of 1 mg/kg/day in the latter study it remains unclear whether effects on the thymus at this dose can be excluded. The effect on the thymus at 5 mg/kg/day in the 90 days oral Roehm and Haas (1999) study is considered to be relevant for a hazard statement. Reduced thymus weights (atrophy) have also been observed in the two prenatal developmental rat studies (Noda 2001) on day 20 of gestation of females treated at 15 and 20 mg/kg. The effects observed on the thymus are consistent with a known class effect of organotins on the immune system.

The threshold level for classification as toxic under DSD is 5 mg/kg. A DSD classification of T; R48/25 is therefore supported by RAC.

Substances that cause significant and/or severe toxic effects of relevance to human health at≤ 10 mg/kg/day in a 90-day study are classified under CLP in Category 1.
The main target organs identified are the central nervous system and the immune system, therefore **nervous system and immune system** should be added as target organs to the hazard statement. A specific concentration limit is not warranted, because the effective dose level or concentration is not 10 times below the guidance value of ≤ 10 mg/kg according to the CLP. In conclusion, RAC agrees with the DS proposal that a classification of **STOT RE 1- H372** is warranted.

4.9 Germ cell mutagenicity (Mutagenicity)

No data available.

4.10 Carcinogenicity

No data available.

4.11 Toxicity for reproduction

Table 12: Summary table of relevant reproductive toxicity studies

Method	Results	Remarks	Reference
First prenatal development study	Dimethyltin dichloride toxic to dams and fetuses at 15 mg/kg/day. Under the conditions of the first prenatal development study, the NOAEL for maternal and fetal toxicity was considered to be 10 mg/kg/day.	Similar to TG OECD 414.	Noda, T. 2001.
Second prenatal development study	Adverse effects to dams were reported at both 20 and 40 mg/kg/day on days 10-12 of gestation. At 40 mg/kg/day, maternal body weight gain and maternal thymus weights were significantly reduced. Maternal thymus weights and adjusted body weight gain were also significantly reduced at 20 mg/kg/day of days 10-12 of gestation.	Similar to TG OECD 414.	Noda, T. 2001.
A first developmental neurotoxicity study	In Ehman's study, developmental neurotoxicity of dimethyl tin dichloride (DMTC) was evaluated in two experiments. In the first study, female Sprague-Dawley rats were exposed via drinking water to DMTC before mating and throughout gestation and lactation. DMTC toxicity was expressed as depressed maternal weight gain, and in the offspring, decreased brain weight, decreased apoptosis and mild vacuolation in the brain of adult offspring, and slower	Similar to the neurotoxicity study of EPA OPPTS 870.6300	Ehman K.D., 2007.

	learning in the water maze.		
A second developmental neurotoxicity study	In a second study, DMTC exposure occurred from gestational day 6 to weaning. The high concentration again depressed maternal weight gain, decreased offspring birth weight and preweaning growth, and decreased brain weight. Learning deficits were observed in the runway at postnatal day 11 (15, 74 ppm) and again in the adult offspring in the water maze (15 ppm).	Similar to the neurotoxicity study of EPA OPPTS 870.6300	Ehman K.D., 2007.

4.11.1 Effects on fertility

No data available

4.11.2 Developmental toxicity

4.11.2.1 Non-human information

The following data were included in the classification proposal discussed by TC C&L.

Species Cell culture	**Route**	**Dose**	**Exp. time**	**Exp. period**	**Observations and Remarks**	**Ref.**
Rat **First study:** 5 groups of 10 pregnant rats each. **Second study:** 8 groups of 8-11 pregnant rats each: 3 groups at 20 mg/kg bw/day during 3 periods of	Gavage Saline	**First study:** 5, 10, 15, and 20 mg/kg bw/day **Second study:** 20 or 40 mg/kg bw/day	-	**First study:** GD 7-17 **Second study:** one of four different periods of gestation (days 7-9, 10-12, 13-15, or 16-17).	**<u>First prenatal development study:</u>** **Test substance:** DMTC, (**Purity** > 99.0%) **Maternal toxicity data in study 1:** -significant reduction in the maternal body weight gain in a dose dependent manner; -significant reduction of maternal food intake; -significant reduction of maternal thymus weights in a dose dependent manner. There was a dose-dependent reduction of maternal body weight gain of pregnant rats treated orally with DMTC during days 7-17 of gestation. Maternal body weight gain was significantly reduced in pregnant rats treated with 15 or 20 mg/kg/day of DMTC (data shown as a graph in the publication). Maternal body weight on GD 20 were also significantly lower in the high dose group (respectively 333g ±26.7, 334g ±21.9, 321g ±21.0, 315g ±9.2, and 252g ±41.1** in the control, 5, 10, 15 and 20 mg/kg groups). Maternal food intake was also significantly reduced by DMTC-treatment at 20 mg/kg/day at GD 11 and between GD 13 and 17 (data shown as a graph in the publication). No other significant	Noda, T. 2001.

gestation (days 7-9, 13-15, 16-17); 4 groups at 40 mg/kg bw/day during 4 periods of gestation (days 7-9, 10-12, 13-15, 16-17) and one control group.					differences in maternal food intake were present in the remaining dose groups. Two animals receiving DMTC-treatment at 20 mg/kg/day died, one on day 18 of gestation and the other on day 19 of gestation. These animals exhibited clinical signs of toxicity, including piloerection, ataxia, perinasal and periocular staining, vaginal bleeding, tremor, and convulsion, for about four days prior to their deaths. No gross pathological changes in the organs of the dead dams were noted at necropsy. No other mortalities were observed in either the control or DMTC-treated groups. Mainly after the day 15 of the gestation, all the animals treated by DMTC at 20 mg/kg/day showed clinical signs of toxicity, including perinasal and periocular staining, piloerection, and ataxia. Three pregnant animals from this group exhibited vaginal bleeding, tremor, and convulsion and two pregnant rats from this group died in the late stage of gestation. No clinical signs of toxicity were observed in the other DMTC-treated groups. There was a dose-dependent reduction in maternal thymus weights, with a significant reduction at 15 and 20 mg/kg/day on day 20 of gestation (respectively 196mg ±37.5, 190mg ±32.6, 168mg ±26.8, 151mg ±13.6* and 45mg ±21.7** on GD20 in the control, the 5, 10, 15 and 20 mg/kg). Maternal brain weight was not affected in any DMTC-treated group. Total resorption was observed in one of the eight living pregnant rats at 20 mg/kg/day on day 20 of gestation. There was a dose-dependent reduction in mean body weight of living fetuses (both sexes), that was significant at 15 and 20 mg/kg/day (respectively 3.5g ±0.20, 3.4g ±0.22, 3.2g ±0.25, 2.9g ±0.16, and 2.2g ±0.46 in males and 3.3g ±0.16, 3.2g ±0.20, 3.2g ±0.27, 2.8g ±0.15, and 2.1g ±0.41 in females of the control, 5, 10, 15 and 20 mg/kg). There was no significant difference in the number of corpora lutea, number of implants, number of living fetuses, or the incidence of post-implantation loss and sex ratio. The incidence of external malformations increased in fetuses from dams exposed to DMTC at 20 mg/kg/day during the days 7-17 of gestation (respectively 0, 0, 0, 2.5 and 22.5% of fetuses at 0, 5, 10, 15 and 20 mg/kg/d). Cleft palate was observed in 21 fetuses from five of seven pregnant rats with living fetuses on day 20 of gestation. In	

					addition to cleft palate, one fetus was associated with general edema and pes varus, and one with general edema. Omphalocele was observed in two fetuses from one dam exposed to 15 mg/kg/day; however, the incidence was not statistically significant. No other external malformations were observed in either the control or DMTC-treated groups. There was a statistically significant increase in the number of fetuses with dilation of the renal pelvis from dams exposed to DMTC at 20 mg/kg/day during days 7-17 of gestation (respectively 0, 0, 1, 4, and 5 fetuses at 0, 5, 10, 15 and 20 mg/kg of DMTC). No other visceral malformations observed were statistically significant. No statistically significant difference in the incidence of skeletal malformations and skeletal variations were observed in either the control or DMTC-treated groups. **<u>Second prenatal development study:</u>** **Test substance:** DMTC, (**Purity** > 99.0%). **Maternal toxicity data in study 2:** -significant reduction of maternal body weight gain; -significant reduction of maternal food intake; Significant reduction of maternal thymus weight and adjusted body weight gain. Significant reductions in maternal body weight gain on days 13, 16, and 17 of gestation and food intake on the consecutive days of gestation after day 12, were reported for pregnant rats exposed to DMTC at 40 mg/kg/day on days 10-12 of gestation (data not shown in the publication). Maternal body weight gain was not significantly reduced in the other DMTC-treated groups or over the whole gestation period (body weight gain of 112±0.16 in controls, 110 ±12.5, 107±18.0, 111±9.0 at 20 mg/kg on GD 7-9, 10-12 and 13-15 and 110±13.1, 95±17.8, 103±12.4 and 102±22.6 at 40 mg/kg on GD 7-9, 10-12, 13-15 and 16-17). Adjusted body weight gain was significantly decreased in rats exposed to DMTC at 20 mg/kg during GD 10-12 and in all rats exposed to 40 mg/kg (47±7.0 in controls, 40±7.4, 35±9.6*, 42±6.5* at 20 mg/kg on GD 7-9, 10-12 and 13-15 and 35±6.0**, 30±9.2**, 33±6.6** and 31±13.3** at 40 mg/kg on GD 7-9, 10-12, 13-15 and 16-17). General behavior among groups, including the control group, was not significantly different. Maternal thymus weights and adjusted body weight gain in pregnant rats exposed to 20	

					mg/kg/day on days 10-12 (maternal thymus weights for the control group: 253 mg ±45.1,) and in every treatment group at 40 mg/kg/day were significantly reduced (maternal thymus weights of respectively 253 mg ±45.1 in the control group, and 220 mg ±22.7, 207 mg ±39.9*, and 217 mg ±15.3 at 20 mg/kg during GD 7-9, 10-12, and 13-15, and 208mg ±37.6*, 190 mg ±36.9**, 182 mg ±32.7**, 172 mg ±45.1** at 40 mg/kg during GD 7-9, 10-12, 13-15 and 16-17). Gravid uterus and maternal body weights were not affected in either the 20 or 40 mg/kg/day groups. Total resorption was observed in one of 10 dams exposed to 40 mg/kg/day during days 7-9 of gestation. Mean fetal body weight was reduced in females from dams exposed to 40 mg/kg/day during days 7-9 (data not shown). No significant differences were reported in the number of corpora lutea, implants, or living fetus. The incidence of post-implantation loss, the sex ratio, and male fetal body weight were not significant in any treatment group (data not shown). There was no significant increase in the incidence of external, skeletal, or visceral malformations at either 20 or 40 mg/kg/day. Cleft palate was not observed in fetuses from dams exposed to DMTC at 20 or 40 mg/kg/day on days 7-9, 10-12, 13-15, or 16-17 of gestation. The numbers of fetuses with skeletal variations, cervical ribs, and/or splitting of the first cervical vertebra arch increased significantly in the groups treated with DMTC at 40 mg/kg/day on days 7-9 and/or days 13-15 of gestation (0, 5* and 4* fetuses with cervical rib respectively in the control group and the groups treated with DMTC at 40 mg/kg/day on days 7-9 and 13-15; 0 and 6* fetuses with splitting of the first cervical vertebra arches respectively in the control group and in the 40 mg/kg/day group at days 7-9). Fetuses with kinked ureter significantly increased in the group treated with DMTC at 40 mg/kg/day on days 16-17 of gestation (0, 3, 1, 2 and 6* fetuses respectively in the control group and in the 40 mg/kg/day group treated on days 7-9, 10-12, 13-15, 16-17).	

***p<0.05, ** p<0.01**

Trials performed in the Experiment 1:

1) Maternal fluid intake and weights:

Overall, consumption increased among all dose groups throughout gestation and lactation. During the first two weeks of exposure (pre-mating), water consumption was significantly decreased in all DMTC-exposed groups (time-by-dose $F_{(9, 87)} = 37.71$, $p<0.0001$). During the first half of gestation, only the high concentration decreased consumption (data not shown, time-by-dose $F_{(18, 180)} = 1.98$, $p=0.013$) but these differences were not significantly different from control throughout the rest of exposure.

Only the high concentration of DMTC altered maternal body weight gain, which was significantly lower than control throughout the exposure (time-by-dose $F_{(18, 180)} = 3.58$, $p<0.0001$).

2) Reproductive parameters:

The overall pregnancy success rate was very low (47 of 120 rats, 39%) as in a previous study. Nevertheless, there was no treatment effect on the number of pregnancies (n=10 control, n=14 at 3 and 15 ppm and n=9 at 74 ppm).

3) Offspring number and growth:

The total number of live pups per litter was: mean ± SEM, control, 14.4 ± 1.0; 3 ppm, 13.3 ± 0.7; 15 ppm, 15.0 ± 0.9; and 74 ppm, 12.8 ± 0.8. There was no significant treatment-by-sex interaction. Three litters in the high-concentration group had one to two dead pups, whereas control litters had none; however this difference was not significant. After culling at PND 1, three litters (one control, two at 74 ppm) lost three to four more pups each.

Average male pup weight per litter was not significantly altered by DMTC exposure (data not shown). Pups weighed at the time of testing for the runway, motor activity and water maze showed no differences from control.

4) Neurobehavioral assessments:

a) *The runway learning test:* PND11 rats pups were food-deprived 10h prior to testing in their dark cycle and were trained to negotiate a runway for a dry suckling reward from its anesthetized mother in the goal box and latency is recorded. Acquisition consisted of 25 alternating reinforced (R), (15 s of dry suckling) and non-reinforced (N), (placement in a holding cage for 15 s) trials. If the pup failed to find the dam within the allotted time, the experimenter guided it down the runway (R) or the animal was immediately placed in the holding cage (N). Extinction, i.e. the blocked access to the dam, immediately followed acquisition.

Several pups in each treatment group failed to learn the task, using the criterion of having at least one latency less than the maximum time of 120 s. However there was no treatment-related difference in the incidence of the non-learners (control: 3 of 12; at 3 ppm: 1of 9; at 15 ppm: 0 of 10 and at 74 ppm: 1 of 9).

Then, extinction trials began on the 26th trial and the maximum time was set at 100 s. When pups reached the criterion of two consecutive 100-second trials, they were no longer tested. The median number of trials required for each dose group was:

control: 18; at 3 ppm: 13; at 15 ppm: 15.5; and at 74 ppm: 24). Although higher in the high-dose group, there were no significant differences in trials to extinction.

b) *Motor activity* data were collected using automated figure-eight chambers. Photocell interruptions (counts) were recorded over 5 minutes intervals of the 30 minutes test session. In experiment 1, motor activity was assessed in males at PNDs 13, 17 and 21 (n=14 control, n=9 at 3 ppm, n=10 at 15 ppm and n=9 at 74 ppm). Total motor activity counts during 30 minutes sessions showed an age-related increase from PND 13 (average of all dose groups: 27.1), PND 17 (average: 80.4) and PND 21 (average: 116.9), but were no treatment-related differences. Analysis of the within-session activity (in 5 minutes intervals) showed that habituation was not evident until PND 21 in all treatment groups.

c) *Morris water maze* is a spatial memory trial where adolescents/young adults' rats (7 weeks old) have to find a hidden platform. Dependant variables included swim speed, latency and path length to find the platform and time spent in the outer edge of the tank or one of the three concentric zones. Only males were tested in the water maze (n=11 control, n=7 at 3 ppm, n=9 at 15 ppm and n=11 at 74 ppm).

   For spatial training, rats learned the fixed position of the platform during 2 trials a day for 9 days. The maximum trial time was 60 s, after which time the observer guided the rat to the platform. The middle dose group showed significantly longer latencies during the first week of training (dose $F_{(3, 31)} = 3.57$, $p=0.025$). In the second week, the low and middle dose groups spent significantly less time in the middle zone (dose $F_{(3, 31)} = 5.79$, $p=0.003$), and in addition, the 15 ppm group spent more time in the outer zone (dose $F_{(3, 31)} = 5.52$, $p=0.004$). The high dose group showed no differences on any of these parameters.

   On the 10^{th} day, the platform was removed for a probe trial and the time spent to search in the correct quadrant was measured over 60 s. A visible probe trial was also conducted using a raised platform of a contrasting color to confirm that the tested animals were not visually impaired. There were no effects on swim speed or search parameters during the probe trials (both the memory probe, platform removed, and the visual trial with the raised platform).

5) Neuropathology:

Neuropathological evaluations were performed in brain male rats (n=6-8/dose at PND 1, n=5-8/dose at PND 12, n=5-9/dose at PND 22, and n=5/dose at adult age, 80-90 days old), in each sections (e.g., olfactory bulb, striatum, cerebral cortex, hippocampus, thalamus, hypothalamus, brainstem, cerebellum). Histopathological alterations were noted in the cerebral cortex of rats sacrificed at PND 22 and as adults. Three of five (60%) adult offspring at 74 ppm and one of five (20%) PND 22 rats at 74 ppm had slight/mild vacuolation of the neuropil of the gray matter of the cerebral cortex. The lower dose groups evaluations showed similar vacuolation at 15 ppm (1 of 5 adults) and 3 ppm (1 of 5 adults). There were no lesions in the offspring at PND 1 or 12, or in the offspring at the lower doses at PND 22. There were no histopathological findings in any major brain region other than the cerebral cortex, and no such findings were observed in control rats at any age.

The cerebral cortical lesion was characterized by 2-4 micron diameter, round vacuoles in the gray matter neuropil in the region of the orbital cortex. On a score of 1 (minimal) to 5 (severe), the rats in the lower dose groups received scores of 1, whereas the high-dose rats received scores of 2 (slight/mild).

6) Brain weights:

PND 1, 12, 22 male brain rats and adults were analysed (n=4-11/dose/age). From PND 12, all subjects came from different litters. Analysis of brain weights revealed an overall effect of dose ($F_{(3, 88)}$ =3.61, p<0.016) but no interaction with age. The data showed significant decreases in the low- and high-dose groups. The low dose was 4% lower and the high dose 8% lower, than controls. The mid dose group average was equal to the control mean.

7) Apoptosis assessment:

In short, apoptosis was quantified using a Cell Death ELISA procedure a few modified, which uses antibodies to bind fragmented DNA characteristic of apoptotic cell death. The bound fragments (i.e. nucleosomes) are then quantified photometrically.

After weighing, brains were dissected into the following regions: brainstem, neocortex, hippocampus and cerebellum, frozen and stored at -70°C. ELISA assays were conducted only on tissues collected at PND 22 (n=3-7/dose/region) and as adults (n=2-4/dose/region).

Significant dose-by-age interactions were observed for the cerebellar (dose-by-age $F_{(3, 27)}$ = 2.93, p=0.05) and cortical (dose-by-age $F_{(3. 27)}$ = 5.79, p=0.003) DNA fragmentation data. Significant decreases of DNA fragmentation were observed only at PND 22 in the cerebellum (15 and 74 ppm) and cortex (all doses). However, these changes did not show a clear dose-response. No differences were seen in adult tissues, but in some cases the sample sizes were not optimal (n=2-4/dose).

Trials performed in Experiment 2:

In the second experiment, eighty-seven pregnant female rats (Sprague–Dawley) (n=21 control, n=22 per DMTC dose groups: 3, 15, and 74 ppm) were treated on gestational day 6 (GD6) and continued through gestation and lactation. Both male and female offspring (one from each litter) were tested in the different neurobehavioral tasks with the exception of the *runway task*, in which only males were tested.

1) Maternal fluid intake and weights:

From the beginning of exposure to the end of gestation, fluid intake was significantly lower in the 15 and 74 ppm dose groups (time-by-dose $F_{(30, 270)}$ = 3.61, p < 0.0001). Only during the second week of exposure, the 3 ppm dose group showed decreased consumption. Intake returned to control levels in all except the high-concentration group during lactation.

No reductions in body weight were evident until lactation, at which time the high-concentration body weight was significantly lower than controls (time-by-dose $F_{(9, 117)}$ = 2.96, p = 0.003).

2) Reproductive parameters:

All of the timed-pregnant females delivered with the exception of one 74 ppm DMTC female. Additionally, one 74 ppm female delivered only six pups and was not used. All of the deliveries occurred when expected.

3) Offspring number and growth:

Five litters had one or two dead pups, but this finding was not related to dose; one litter at 3 ppm, and four litters at 15 ppm.

Body weight pups changes during the lactation period showed a significant dose-by-sex interaction ($F_{(3, 69)} = 3.0$, $p=0.037$). Males in the high-concentration group weighed significantly less than controls throughout lactation, and in the same group, the females weighed less with significance only at PND 17 and PND 21. In contrast, no treatment effect on body weight was measured weekly after weaning, or at the time of behavioural testing. Thus, the high concentration suppressed growth during lactation in the second study, but not the first study.

4) Neurobehavioral assessments:

a) Runway testing: A different training schedule was used in Experiment 2. Pups (n=20/dose except n=19 at 74 ppm) were food-deprived for 8 h and then tested during their light cycle. Testing began with a preliminary training session of 5 massed reinforced (R) trials, followed by a 2 min retention interval in the holding cage. There were then 25 acquisition trials in which reinforced (R) and non-reinforced (N) trials alternated in blocks of 5 trials. The maximum time allowed for each trial was 100 second.

The percentage of pups that failed to learn to negotiate the runway increased in a dose-dependent manner (control: 3 of 20; 3 ppm: 5 of 20; 15 ppm: 6 of 20; and 74 ppm, 6 of 19), with no statistical significance.

The control and the low-dose group showed significant decreasing slopes ($p's<0.04$ for all) for each R-trials. In contrast, the 15 ppm dose group did not show decreased latencies on any of the R-trials and the high-dose group showed a decreasing slope ($p=0.008$) only during the last block of R-trials.

b) Motor activity:

Only PND 17 male and female offspring were tested (one male and one female from each litter; n=21 for the control and at 15 ppm, n=20 at 3 ppm, n=17 at 74 ppm). There were no group differences in PND 17 motor activity and no interactions with sex. Total counts for each group (sexes combined, mean ± SEM) were: control, 115.4 ± 7.8; 3 ppm, 114.2 ± 5.6; 15 ppm, 121.5 ± 9.2; and 74 ppm, 119.0 ± 8.8). Unlike in Experiment 1, habituation was evident in all treatment groups at PND 17.

c) Spontaneous alternation (exp 2 only):

Spontaneous alternation was measured on PND 25 using a Plexiglass T-shaped apparatus. Pups were placed in the stem for a 30 s acclimation, after which time, the gate was raised allowing the rat to enter either arm, and to explore only the 2 opposing arms for 5 min. All arm entries were counted as the measure of motor activity, whereas alternation was considered when the rat left one arm and entered the other. Both males and females were tested at 10/dose.

The overall dose effect did not reach significance (dose $F_{(3, 36)} =2.48$, $p=0.077$). The number of arm visits was (in average): male and female control group: 10.5; males at 15 ppm: 6.7 ± 1.6 and males at 74 ppm: 11.7 ± 0.7. The percent of

alternations showed no significant difference across groups or gender (mean ± SEM): control, 84.5 ± 2.9; 3 ppm, 84.3 ± 2.5; 15 ppm, 86.1 ± 2.4; and 74 ppm, 78.7 ± 2.6.

d) Morris water maze:

Unlike in Experiment 1, 12 weeks old rats were tested. Both males and females (one from each litter) performed the trial (n=10/sex/dose).

As in Experiment 1, the 15 ppm (middle) dose group had significantly higher latencies to learn the platform position (dose $F_{(3, 71)} = 3.1$, p=0.032).

In terms of the spatial pattern of swimming on days 2 and 3, all dose groups spent significantly more time in the outer zone than in the middle zone. This propensity for the outer zone persisted in the middle dose group into the second week of training (dose $F_{(3, 71)} = 7.44$, p=0.0002), and was significant for both males and females. The tracings from middle dose rats showed they spent more time in outer zone, and less time in the middle zone of the tank. Analysis of the memory probe again revealed less time in the middle zone (dose $F_{(3, 71)} = 3.21$, p=0.028) in both males and females of the middle dose group. There were no differences across dose groups in swim speed or latency to find the visible platform.

5) Neuropathology:

Brains were prepared and examined as described for Experiment 1, but only adult rats (both males and females) were used (n=10/dose/sex, except n=9 in the 15 ppm males group).

One male offspring at 74 ppm had a single neuron in the midbrain with central chromatolysis. There were no others axonal lesions and no others rats at this dose level exhibited the same lesions. Thus, significance of this finding in a single neuron in a single treated rat remains undetermined.

6) Brain weight:

PND12, 22 and adults male brain rats were analysed (n=7-9/dose/age). From PND12 on, all subjects came from different litters. As in the first experiment, there was an overall effect of dose ($F_{(3, 67)} =4.05$, p=0.01) in male rats. Collapsed across age, only the high dose group showed a significant decrease of 4%.

7) Apoptosis:

Tissues were collected from male rats only as described for experiment 1 on PND 12, 22 and as adults, with n=6-8/dose/region (brainstem, neocortex, hippocampus and cerebellum).

No treatment effect at PND 12 was observed for the brainstem, but significant increases relative to control at PND22 and decreases in adults (dose-by-age interaction ($F_{(6, 60)} = 11.90$, p<0.0001). These significant effects were seen in the mid and high dose groups. In addition, cerebellar data revealed small significant increase in DNA fragmentation (dose-by-age $F_{(6, 60)} =3.36$, p=0.006) at PND 12, but only at the high dose (means ± SE: control, 1.0 ± 0.07; 3 ppm, 1.30 ± 0.07; 15 ppm, 1.06 ± 0.04; 74 ppm, 1.07 ±0.08).

4.11.2.2 Human information

No data available.

4.11.3 Other relevant information

The study of Noland et al. (1983) was not included in this dossier at the time of the proposal for the harmonised classification and labelling to the TC C&L in October 2006. Nevertheless, this study is interesting for the developmental neurotoxicity analyse of dimethyltin dichloride.

Studies were conducted with seventy-day-old Sprague-Dawley females' rats to determine whether DiMethylTin diChloride (DMTC) was absorbed by the dam and transferred across the placenta to foetal blood and brain tissue:

In the first study, three groups were formed. The first group received the DMTC at 40 mg/L in their drinking water (n = 13). The second group received identical levels of tin as stannous chloride (n = 13) and a third group received distilled water (n = 12), and served as the control group. The exposure began 2 weeks prior to breeding and continued through gestation. At birth and prior to the first nursing, the pups were removed from the dams and sacrificed. Blood samples pups were taken and brains pups were removed. Dams weight gain and water consumption were measured and blood samples were taken.

The tin content of blood from control dams and from dams given stannous chloride was not different while the tin content from those given DMTC was significantly higher than both of the other two groups ($X2 = 24.7$, $df = 2$, $p < 0.0001$). Similarly, the tin content in blood from pups of dams given DMTC was significantly higher than blood from pups of either of the other two groups ($X2 = 24.7$, $df = 2$, $p < 0.0001$). In the pup brain of dams exposed to DMTC, the tin level was significantly higher than controls or those given stannous chloride ($X2 = 23.1$, $df = 2$, $p < 0.0001$).

DMTC is therefore absorbed by the rat dam, transferred by placenta to the foetus and arrives in the brain of the prenatal animal.

In a second step, a cross-fostering study was conducted. Two groups of rats were tested, one treated with DMTC in drinking water (40 mg tin/L) and the no treated control. At birth, before first nursing, pups born to DMTC-exposed dams were placed either with control dams for rearing (n = 8) (DM/CT) or with another DMTC-exposed dams (n = 8) (DM/DM). Pups born to control dams were placed either with DMTC-exposed dams (n = 8) (CT/DM) or with another control dam (n = 8, CT/CT). Brain and blood samples were collected from the remaining control (n = 4) and DMTC-exposed litters (n = 4) on post natal days (PND) 10 and 21.

The levels of tin in pups from DMTC-exposed dams ($X \pm SE = 5.88$ µg/g ± 0.83) was significantly higher than that of controls ($X \pm SE = 0.115 \pm 0.04$; $p = 0.005$).

The highest levels of tin in blood were reached at birth in gestationally exposed pups. Then, at PND 10, blood tin levels decreased rapidly in both prenatally exposed groups (i.e. in DM/DM and DM/CT groups). Pups exposed only postnatally (CT/DM) had blood levels of tin significantly lower than the DM/DM and the DM/CT animals. This results show that DMTC is mainly transferred to the pups during the gestation.

Tin levels in the brains of gestationally exposed pups were again highest at birth and different from controls ($p = 0.004$). At PND 10, the DM/DM pups demonstrated significantly higher levels of tin in the brain than the other groups ($f = 19.42$; $df = 3.12$; $p = 0.01$). At PND 21, the DM/DM group was significantly higher than the CT/DM group, which was higher than either the CT/CT or the DM/CT group ($f = 9.445$; $df = 3.21$; $p = 0.05$).

The greatest decrease seen in the pups from the DM/CT group, indicate a rapid clearance of the tin from the blood and brain.

During the post natal period, the DMTC follows the same pattern of decreasing concentration in pup brain and pup blood, indicating relatively unimpeded brain-to-blood transfer, as is expected in animals with immature blood-brain barriers.

In the third study, a 14C-DMTC tracer was administered by intubation to the 19 days pregnant dams. Then, dams were sacrificed at 5 minutes, 15 min, 30 min, 1h, 2h, 6h and 24h (n = 4 at each interval). Brains and blood samples were taken for analysis. The fetuses were removed in order to take their blood and brain samples.

The highest measured levels of 14C-DMTC in the blood were recorded at 1h for the dams and at 6h for the pups while the levels in the brain continued to increase through 24h for both the dams and the pups. The 14C-DMTC was readily absorbed into both dam blood and brain and fetal blood and brain. However, at 6h after exposure, the fetal blood 14C level represented 16% of dam blood level although fetal brain 14C levels represented 167% of dam brain 14C concentrations. This 10-fold higher brain/blood ratio for fetal might be explained by the immaturity of the "blood-brain barrier" or by the transfer of a more available 14C-non-Sn-containing metabolite than 14C-DMTC.

The results of this study have demonstrated that DMTC is absorbed in the gastrointestinal tract of the dam and DMTC is transferred across the placenta to fetal blood and brain tissue. The majority of the tin is transferred from the pups prenatally, during gestation rather than lactation.

4.11.4 Summary and discussion of reproductive toxicity

In the first study of Noda (oral treatment on days 7-17 of gestation), severe maternal toxicity occurred at the high dose of 20 mg/kg/day. These clinical signs of toxicity are vaginal bleeding, tremors and convulsions [30%], ataxia and other clinical signs of toxicity (severe thymus atrophy) [100%] and they generally appear after the 15th day of gestation. Oral administration of DMTC at 20 mg/kg/day resulted in the death of two pregnant rats [20%], caused by the DMTC treatment. Total resorption was observed in one of eight living pregnant rats, which exhibited all these clinical signs of toxicology at this level dose in the late stage of gestation.

Besides, administration of DMTC at 20 mg/kg/day caused cleft palate in 21 fetuses (22%). The teratogenicity of DMTC can be discussed because of the severe maternal toxicity at this dose level. As cleft palates are a rare and serious malformation, it cannot be considered as secondary to maternal toxicity and it cannot be discarded. Moreover, mean body weight in living fetuses of both sexes decreased in a dose-dependent manner with significance at 15 and 20 mg/kg/day.

In order to reduce maternal toxicity, shorter periods of DMTC treatment (two or three consecutive days at one of four different periods of gestation) and relative high doses of DMTC were chosen in a second study. The highest dose (40 mg/kg/day) of DMTC caused slight maternal toxicity as indicated by the reductions of the adjusted body weight gain and the thymus weight. No significant increase in the incidence of external, skeletal and visceral malformations were observed at either dose in any treatment period group, and no cleft palate was found. Fetal body weight was also unaffected.

In Ehman's study, developmental neurotoxicity of DiMethylTin dichloride in drinking water (DMTC) was evaluated in two experiments. In the first study, female Sprague-Dawley rats were exposed via drinking water to DMTC before mating and throughout gestation and lactation. DMTC toxicity was expressed as depressed maternal weight gain, and in the

offspring, decreased brain weight, decreased apoptosis and mild vacuolation in the brain of adult offspring, and slower learning in the water maze.

In a second study, DMTC exposure via drinking water occurred from gestational day 6 to weaning. The high concentration again depressed maternal weight gain, decreased offspring birth weight and preweaning growth, and decreased brain weight. Learning deficits were observed in the runway at postnatal day 11 (15, 74 ppm) and again in the adult offspring in the water maze (15 ppm).

The effect observed in the runway testing was identified only in experiment 1 but it may be due to the lower number of tested pups. In the second experiment, the 74 ppm dose-group succeed in learning as there are decreased latencies in the last block of reinforced-trials, although the 15 ppm dose-group failed to learn in all the reinforced trials. However, only the 15 ppm dose-group shows a decreased latency during the non-reinforced (extinction phase), which seems to be an aberration. *So, learning was not observed during any reinforced-trial blocks in the 15 ppm group, but was only achieved at the last set of trials in the 74 ppm group.* The absence of dose-response therefore questions the significance of this finding. It is however noted that the trial does not follow the test guideline 426 of the OECD on the neurotoxicity for the development: on the one hand, the test was performed only at PND 11 although it also has to be done at PND 25 and at adult age; on the other hand, a too small number of pups was tested in the experiment 1 (n= 11 control, 9 at 3 and 74 ppm, and 10 at 15 ppm) instead of 10 rats by sex. Moreover, it is not known whether each tested pup comes from different litters as it is recommended in the test guideline 426. It is therefore difficult to conclude on the presence or the absence of a neurotoxic effect.

In the Morris water maze, the 15 ppm-group shows longer latencies to reach the platform than the 74 ppm-group in the first week for the experiment 1 and in the second week for the experiment 2. Thus, the effect in the 15 ppm group seems to be reproducible but it is not observed at the higher dose. In the both experiments, the 15 ppm group spent more time in the outer zone than in the middle one. According to the TG 426 (OECD), the trials have to be performed on 10 animals by sex and by litter, at PND 25 and adult age. However, in the experiment 1, there are only males rats, and a too small number of pups was tested (n= 11 control, 7 at 3 ppm, 9 at 15 ppm, and 11 at 74 ppm). It may explain that effect at higher may not have been detected in experiment 1. In experiment 2, the adequate number of pups was tested but it is not known whether they come from different litters. These uncertainties make it difficult to come to a clear conclusion.

DNA fragmentation due to apoptosis was lower at PND 22 in the experiment 1 whereas an increase was observed at PND 22 (in 15 and 74 ppm groups) in the experiment 2. However, in the experiment 1, the sample sizes were not optimal (n= 2-4/dose), and in the experiment 2, only males are tested. The between-subject variability observed could be caused by the extended study across the ages.

Decreased brain weight was observed at 74 ppm in the both experiment although only males were affected in the second experiment. Histopathological alterations in the brain of offspring of dams exposed to DMTC were noted in the cerebral cortex of rats sacrificed at PND 22 and as adults in experiment 1. Slight/mild vacuolation of the neuropil of the gray matter of the cerebral cortex were observed in 60% of adult offspring at 74 ppm and 20% of PND 22 rats at 74 ppm. Evaluations of the lower dose groups (at 3 and 15 ppm) showed similar vacuolation.

Moreover, in the repeated dose toxicity study in rats, neurobehavioral effects and similar neuropathological lesions were observed at 25 ppm, 75 ppm and 200 ppm (Elf Atochem, 1996), and at 200 ppm in rats (Rohm & Haas Co, 1999).

Overall, the results of both experiments demonstrate a reproducible effect of 15 ppm perinatal DMTC exposure on spatial learning. Changes in expression of apoptosis, brain weight and the occurrence of neuropathological lesions also indicate potential neurotoxicity of DMTC.

The study of Ehman does not follow the TG 426 of the OECD concerning the number and the gender of animals tested and the neurobehavioural effects observed in both the runway testing and the morris water maze have to be confirmed by other studies.

4.11.5 Comparison with criteria

The CLP criteria for classification in Repr.2 are as follow:

*"Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or **experimental animals**, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or **on development**, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification. Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects."*

Overall, based on animal studies:

- DMTC induced cleft palates on the fetuses at 20 mg/kg/day, in presence of severe maternal toxicity at this high dose level (Noda 2001, first experiment). Cleft palates are a rare and serious malformation and it is therefore not considered as secondary to maternal toxicity. However, no significant increase in the incidence of cleft palates or other external, skeletal and visceral malformations were observed in a second study at similar or higher dose levels although the substance was administered for shorter durations but covering the whole embryogenesis period. Malformations were also not observed in Ehman 2007 but it may be due to lower dosage (high dose between 4 and 12 mg/kg). Therefore, considering the absence of reproducibility in both experiment of Noda 2001, the evidence is not considered sufficient to place the substance in category 1B.

- DMTC induced a decrease in fetal body weight at 15 and 20 mg/kg (Noda 2001, first experiment). At these doses, maternal toxicity was also observed but the magnitude of fetal weight decrease (-17% and -37% in male pups and -15% and -34% in female pups) was more important that the magnitude of maternal weight decrease (-5% and -24%). No effect on fetal body weight was observed in a second study at similar or higher dose levels although the substance was administered for shorter durations and induced maternal toxicity as evidenced by significant decrease in maternal adjusted body weight gain. In Ehman 2007, a decrease in fetal body weight was observed only at high dose (7-12 mg/kg) in the second experiment during lactation when maternal weight was also significantly decreased. The link between foetotoxicity and maternal toxicity is therefore likely and cannot be totally excluded. Therefore, the evidence is not considered sufficient to place the substance in category 1B.

- DMTC showed a developmental neurotoxic potential in Ehman 2007. The absence of reproductibility of the effects observed in the runaway and water maze tests does not allow giving a clear conclusion. Besides, the study is not consistent with guideline requirement, which raise further uncertainties on the significance of the result. However, it is noted that histopathological lesions observed only in experiment 1 are similar to those reported in adult exposed to DMTC and in foetuses exposed to MMTC, which support that this effect is specific to methyltin exposure and is treatment-related. However, due to the uncertainties discussed above, the evidence is not considered sufficient to place the substance in category 1B.

A classification Repr. 2 H361d" is proposed for DMTC (Reprotox Cat 3 Xn R63 according to Directive 67/548/EEC). .

Classification in Repr. Cat.1A is not appropriate as it should be based on human data and no human data specific of DMTC are available.

4.11.6 Conclusions on classification and labelling

A classification **"Repr. 2 H361d"** is proposed (**Repr. Cat. 3, Xn R63** according to Directive 67/548/EEC).

Data are available only by oral route and the route of exposure cannot be specified in the hazard statement.

RAC evaluation of Reproductive toxicity

Summary of Dossier submitter's proposal
Two prenatal developmental studies in rats (gavage) similar to OECD 414 (with some deviations on group size and exposure) are included in the CLH report (Noda *et al*. 2001). In addition, two developmental neurotoxicity studies in rats (drinking water) similar to EPA OPPTS 870.6300 are presented (Ehman, 2007). One supporting study (Noland 1983) is included to demonstrate the transfer of DMTC to blood and brain of foetuses from exposed mothers during gestation. Based on effects seen in the prenatal development and neurotoxicity studies, the DS proposed a classification of Repr. 2 – H361d according to CLP (DSD: Repr. Cat. 3; R63). Effects on fertility were not examined in the CLP report.

Comments received during public consultation
Comments were received from four MS during public consultation. Two of them supported the proposal while one suggested considering classification as Repr. 1B – H360D. The fourth MS suggested that no classification was warranted. Further details, including the dossier submitter's response, can be found in the RCOM.

RAC assessment and comparison with criteria
Evaluation of toxicity for reproduction is based on two prenatal development studies (both in Noda, 2001) and two developmental neurotoxicity studies (both in Ehman, 2007).
In the first study by Noda (2001) (oral treatment on days 7-17 of gestation at 0, 5, 10, 15, and 20 mg/kg bw/day), severe maternal toxicity occurred at the high dose of 20 mg/kg/day. These clinical signs of toxicity were vaginal bleeding, tremors and convulsions (30%), ataxia and other signs of toxicity (severe thymus atrophy) (100%) and they generally appeared after the 15th day of gestation. Oral administration of DMTC at 20 mg/kg/day resulted in the death of two pregnant rats (20%). At this does, total resorption was observed in one of eight living pregnant rats, which exhibited all these clinical signs of toxicity in the late stage of gestation. DMTC at 20 mg/kg/day also caused cleft palate in 21 foetuses (22%). The teratogenic effects occurred in the presence of severe maternal toxicity. Mean body weights of living foetuses of both sexes decreased dose-dependently with statistical significance at 15 and 20 mg/kg/day.

In the second study of Noda (2001) shorter periods of DMTC treatment (two or three consecutive days at one of four different periods of gestation) and daily doses of 20 or 40 mg DMTC/kg bw were chosen in order to reduce maternal toxicity. The highest dose (40 mg/kg/day) caused slight maternal toxicity as indicated by the reductions of the adjusted body weight gain and the thymus

weight. No significant increase in the incidence of external, skeletal or visceral malformations were observed at either dose in any treatment period group, and no cleft palate was found. Foetal body weight was also unaffected.

In developmental neurotoxicity studies (Ehman 2007) the effect of DMTC in drinking water was evaluated in two experiments. In the first study, female Sprague-Dawley rats were exposed daily via drinking water to 0, 3, 15, and 74 ppm DMTC before mating and throughout gestation and lactation. Reduced maternal weight gain occurred at the highest dose. In the offspring, decreased brain weight, decreased apoptosis and mild vacuolation in the brain of adult offspring, and slower learning in the water maze were observed, although the latter was not seen at the highest concentration. In the second study, DMTC exposure via drinking water occurred from gestational day 6 to weaning. The high concentration depressed maternal weight gain, decreased offspring birth weight and preweaning growth, and decreased brain weight. Learning deficits were observed in the runway at postnatal day 11 at 15, 74 ppm and again in the adult offspring in the water maze at 15 ppm.

However, these effects occurred either in one study only, had no dose response relationship or, occurred in the presence of maternal toxicity.

In conclusion

- DMTC induced cleft palates in the foetuses at 20 mg/kg/day, in the presence of severe maternal toxicity at this high dose level (Noda, 2001, first study). No significant increase in the incidence of cleft palates or other external, skeletal or visceral malformations were observed in a second study at similar or higher dose levels although the substance was administered for shorter durations but covering the whole embryogenesis period. Maternal toxicity and malformations were not observed in the Ehman (2007) studies, which may be due to lower dosage (high dose between 4 and 12 mg/kg). Therefore, considering the absence of reproducibility in both studies in Noda (2001) and since no skeletal malformations seen in the Ehman (2007) studies, the occurrence of cleft palate in one study in the presence of severe maternal toxicity is not considered sufficient to place the substance in category 1B.

- DMTC induced a decrease in foetal body weight at 15 and 20 mg/kg (Noda, 2001, first study). At these doses, maternal toxicity was also observed but the magnitude of foetal weight decrease (-17% and -37% in male pups and -15% and -34% in female pups) exceeded the magnitude of maternal weight decrease (-5% and -24%). These effects did not occur in the second study at similar or higher dose levels although the substance induced significant decrease in maternal adjusted body weight gain. In Ehman (2007), a decrease in foetal body weight was observed only at high dose (7-12 mg/kg) in the second experiment during lactation when maternal weight was also significantly decreased. The link between foetotoxicity and maternal toxicity is therefore likely and cannot be totally excluded. Therefore, the evidence is not considered sufficient to place the substance in category 1B.
- DMTC showed developmental neurotoxic potential in Ehman (2007). The absence of reproducibility of the effects observed in the runaway and water maze tests does not permit a clear conclusion to be drawn. Besides, the studies are not consistent with guideline requirements which raises further uncertainties as to the significance of the results. Due to these uncertainties, the evidence is not considered sufficient to place the substance in category 1B.

The effects reported above support classifying DMTC as a reproductive toxicant for effects seen on development. Due to the inconsistencies in these effects, RAC agrees with the original DS proposal and considers classification of DMTC in category Repr. 2 H361d (DSD: Reprotox Cat 3 Xn R63) as justified.

As the dossier submitted did not address the fertility endpoint, RAC did not evaluate this aspect of reproductive toxicity.

4.12 Other effects

Not covered in this dossier.

5 ENVIRONMENTAL HAZARD ASSESSMENT

Not evaluated in this dossier.

6 OTHER INFORMATION

No other information.

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8 ANNEXES

ANNEX I

Collection of discussions of DMTC and DMT(EHMA) classifications at ECB

For health effects, DMTC and DMT(EHMA) classifications were discussed and concluded at the Technical Committee of Classification and Labelling (TC C&L) in October 2006.

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

Dimethyltin dichloride, DMTC (F048) [1]

EC number: 212-039-2, CAS number: 753-73-1

Classification proposal : [Repr. Cat. 3; R63 - T+; R26 - T; R25 - Xn; R21 - T; R48/23/24/25 - C; R34 - R52/53]

ECBI/25/06 French C&L proposal, as prepared by IND, for Dimethyltin dichloride, DMTC

FR presented the classification proposal.

DE asked about the substances, whether these complex substances were already diluted in solution in the studies and whether you need to go back and understand the toxicity of the complex substance itself.

IND replied that the CAS numbers are for the purified substances. All these substances are produced as mixtures and we have used the historical data as if it was the purified substance. We understand this might be a discussable method, but it is pragmatic and we assume that at least this would never lead to under classification and that is the reason why we have decided to use it.

Acute toxicity:

The **TC C&L experts** agreed to classify DMTC with T+; R26, T; R25 and Xn; R21

Corrosivity:

The **TC C&L experts** agreed to classify DMTC with C; R34

Long term toxicity:

T; R48/23/24/25 was proposed. **DE** supported classification for the oral route only as the other routes were read across from acute toxicity and the substance was corrosive. Especially that made it questionable to include longer term effects by inhalation. **NL** did not agree to the reading across for the dermal route.

BE and **DE** did not support reading across from acute to long term toxicity for the inhalation route.

It was agreed not to classify with T; R48/23/24.

The **TC C&L experts** agreed to classify DMTC with T; R48/25.

Reprotoxicity:

There was a proposal to classify for developmental toxicity: Repr. Cat. 3; R63 based on evidence for the substance and as presented by **F**.

R63 was agreed without a long discussion. **N** and **DE** expressed agreement, no MS expressed disagreement.

Conclusion:

The TC C&L agreed to classify **Dimethyltin dichloride, DMTC** with **Repr.Cat. 3; R63 – T+; R26 – T; R25- 48/25 - Xn ; R21 – C; R34.** The corresponding labelling would then be the symbol: T+, and the R-phrases: 21-25-26-34-48/25-63 and the S-phrases: 26-28-36/37/39-45. *(Classification for environmental effects has to be discussed in January 2007.)*

[...]

Dimethyltin bis(2-ethylhexyl- mercaptoacetate, DMT (EHMA) (F050) [3]

EC number: 260-829-0, CAS number: 57583-35-4

Classification proposal : [Repr. Cat. 3; R63 - T; R24 - Xn; R22 - T; R48/23/~~24~~/25 - Xi; R43 - R52/53]

ECBI/24/06 ethylhexyl-	French C&L proposal, as prepared by IND, for Dimethyltin bis(2-
	mercaptoacetate, DMT (EHMA)
ECBI/24/06 Rev. 1 mercaptoacetate,	French revised C&L proposal for Dimethyltin bis(2-ethylhexyl-
	DMT (EHMA)

Acute toxicity:

The T; R24 proposal was withdrawn due to availability of additional data supporting no classification for the dermal route.

Xn; R22 was agreed.

Sensitisation:

The **TC C&L experts** agreed to classify DMT (EHMA) with R43 without further discussion.

Long term toxicity:

The **TC C&L experts** agreed to classify DMT (EHMA) with T; R48/25 based on the DMTC data due to the DMTC being a hydrolisation product of DMT (EHMA). The long- term toxicity proposed by the other routes was not agreed.

Reprotoxicity:

Repr. Cat. 3; R63 was proposed on basis of the DMTC data because DMTC is a hydrolisation product of DMT (EHMA). This was agreed by the TC C&L.

Conclusion:

The **TC C&L** agreed not to classify **Dimethyltin bis(2-ethylhexyl- mercaptoacetate, DMT (EHMA)** T; R24; T; R48/23 and T; R48/24. The TC C&L agreed to classify **Dimethyltin bis(2-ethylhexyl- mercaptoacetate, DMT (EHMA)** with Repr. Cat. 3; R63 - T; R48/25 - Xn; R22 – R43. The corresponding labelling would then be the symbol: T, and the R-phrases: 22-43-48/25-63 and the S-phrases: 36/37-45. *(Classification for environmental effects has to be discussed in January 2007.)*