Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

Dimethyltin dichloride

EC Number: 212-039-2

CAS Number: 753-73-1

CLH-O-0000001701-83-03/F

Adopted

30 November 2012

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OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **Dimethyltin dichloride**

EC Number: **212-039-2**

CAS Number: **753-73-1**

The proposal was submitted by **France** and received by RAC on **14 February 2012.**

In this opinion, all classifications are given firstly in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS) and secondly, according to the notation of 67/548/EEC, the Dangerous Substances Directive (DSD).

The proposed harmonised classification

	CLP	**DSD**
Current entry in Annex VI of CLP Regulation (EC) No 1272/2008	No entry	No entry
Proposal by dossier submitter for consideration by RAC	Acute Tox.3 - H301 Acute Tox.3 - H311 Acute Tox.2 - H330 Skin Corr.1B - H314 Repr. 2 - H361d STOT RE1 - H372 (nervous system)	T; R25 Xn; R21 T+; R26 C; R34 Repr. Cat. 3; R63 T; R48/25
Resulting harmonised classification (future entry in Annex VI of CLP Regulation) as proposed by dossier submitter	Acute Tox.3 - H301 Acute Tox.3 - H311 Acute Tox.2 - H330 Skin Corr.1B - H314 Repr. 2 - H361d STOT RE1 - H372 (nervous system)	T; R25 Xn; R21 T+; R26 C; R34 Repr. Cat. 3; R63 T; R48/25

PROCESS FOR ADOPTION OF THE OPINION

France has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation*** on **14/02/2012.** Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **30/03/2012**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Helmut Greim**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation.

The RAC opinion on the proposed harmonised classification and labelling was reached on 30 **November 2012** and the comments received are compiled in Annex 2.

The RAC Opinion was adopted by **consensus**.

OPINION OF THE RAC

The RAC adopted the opinion that **Dimethyltin dichloride (DMTC)** should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard state-ment Code(s)	Pictogram, Signal Word Code(s)	Hazard state ment Code(s)	Suppl. Hazard statement Code(s)		
050-029-00-8	Dimethyltin dichloride	212-039-2	753-73-1	Repr. 2 Acute Tox.3 Acute Tox.3 Acute Tox.2 Skin Corr. 1 STOT RE1	H361d H301 H311 H330 H314 H372 (nervous system, immune system)	GHS05 GHS06 GHS08 Dgr	H361d H301 H311 H330 H314 H372 (nervous system, immune system)	EUH071		

Classification and labelling in accordance with the criteria of DSD

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
050-029-00-8	Dimethyltin dichloride	212-039-2	753-73-1	Repr. Cat. 3; R63 T+; R26 T; R24/25-48/25 C; R34	T+; C R: 24/25-26-34-48/25-63 S: (1/2-)26-28-36/37-39-45-63		

SCIENTIFIC GROUNDS FOR THE OPINION

Human health hazard assessment

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.

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.

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.

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).

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.

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.

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.

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.

ANNEXES:

Annex 1 Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the dossier submitter; the evaluation performed by RAC is contained in RAC boxes.

Annex 2 Comments received on the CLH report, response to comments provided by the dossier submitter and RAC (excl. confidential information)