Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Dimethyltin dichloride (DMTC)

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

CLH-O-0000001701-83-03/A2

Adopted

30 November 2012

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

[ECHA has compiled the comments received via the internet that refer to several hazard classes and has entered them under each of the relevant categories/headings as comprehensively as possible. Please note that some of the comments might occur under several headings, when splitting the information provided is not reasonable.]

Substance name: Dimethyltin dichloride (DMTC)
CAS number: 753-73-1
EC number: 212-039-2

General comments

Date	Country/ Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
26/03/2012	Germany/ MSCA	DE understands that the dossier submitter intended to submit a dossier for DMTC. Therefore, it is totally clear why in chapter 1.1 of the IUCLID DMTC is presented as a mono-constituent-substance. However, in chapter 1.2 of the IUCLID file and chapter 1.2 of the report it becomes very likely that more than one constituent is present in a concentration between >=10 - < 80%. In the dossier it is stated that "Dimethyltin dichloride is intentionally manufactured as a mixture with monomethyltin trichloride (CAS 993-16-8)". This implies that DMTC is a multi-constituent substance with monomethyltin trichloride as a constituent. The correct naming would then be "reaction mass of DMTC and monomethyltin chloride", and monomethyltin trichloride should be given as a constituent. Also the CAS- and EC-number of the multi-constituent-substance should be used. Furthermore it should be clarified whether water is present as a solvent or to stabilize the substance. In the first case, water should not be included in the mass balance, since it was added intentionally. In the second case water would be a constituent, since it is required for to preserving the stability of the substance. Having these points in mind DE would like to ask for a clarification of	As suggested by the ECHA in the accordance check, DMTC is considered as a mono-constituent substance although all the studies are achieved with a mixture of DMTC and MMTC (with the DMTC always in proportions superior to the MMTC). Besides, MMTC has already been classified recently (Repro 2, H360d), so that it does not need to be studied again, but a read across could be done with this substance. We do not have more information on the substance identification.	noted

Date	Country/ Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		the substance ID.		
26/03/2012	Germany / TIB Chemicals AG	In the CLH report "Proposal for Harmonised Classification and Labelling" for dimethyltin dichloride, DMTC form ANSES (on behalf of the French MSCA) we find data lacking on acute human toxicity. In literature there are reports available, which are cause for increasing concern on this substance group. Specific information see attachment *ECHA comment: The attachment documentmethyltincompounds V2.pdfhas been copied into the section "Other Hazard and endpoints". Attachment no. 1.*	We answered in the section "Other hazard and endpoints" below.	noted
29/03/2012	Belgium/ MSCA	In table 3, Acute Tox. 4; H312 should be replaced by Acute Tox. 3; H311 We understand from table 1 that DMTC is present in DMTC/MMTC mixture in concentration ranging from 50 to 99% (by weight). This could be added in Table 6. What do you mean with a concentration range of 50-99% for di/monomethyltin mixture as impurity in table 7? Why do you include the BIBRA study (1998) related to 2-EHMA in section 4.11.2.1. On page 36, why do you include a justification of read-across between DMTC and DMT(EHMA)? On page 43, section 4.11.4, why do you mention the study of Nodal? Isn't it the study of Noda. Same comment on page 9, section 1.5. On page 46, it is written "The link between foetotoxicity and maternal toxicity is therefore likely but cannot be totally excluded." Maybe "and" instead of "but" could be more appropriate.	It has been corrected. Thank you for your relevant remark. However, it has already been discussed with ECHA: DMTC is considered as a monoconstituent substance and DMTC/MMTC mixture is considered as impurity. We omitted to delete BIBRA study. BIBRA study has been deleted. Read Across has been deleted. "Noda" has been corrected. Modification taken into	Noted Noted Noted Noted noted

Date	Country/ Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		On page 46, in the last sentences of section 4.11.5, we suggest to suppress "(see separate CLH dossier)" and we question the presence of the last sentence (more related to the DMT(EHMA) dossier).	account. It has been suppressed.	
30/03/2012	Sweden/ MSCA	SE supports classification of DMTC (CAS No 753-73-1) as Acute Tox 3, H301; Acute Tox 2, H330, and STOT RE 1, H372 (with nervous system as main target organ) as specified in the proposal. SE agrees with the rationale for classification into the proposed sub category.	Thank you.	noted
30/03/2012	Netherlands/ MSCA	As the classification proposal for DMTC is based on the same information as DMT(EHMA) the same comments regarding developmental toxicity are presented.	ok	noted

Carcinogenicity – no comments received
Mutagenicity – no comments received

Toxicity to reproduction

Date	Country/ Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
26/03/2012	Germany/ MSCA	Editorial: The citation of the investigations of Noda, T. (2001) should be corrected from Nodal to Noda throughout the document Page 9, second last paragraph: Please add to the signs of maternal toxicity listed in brackets also death and severe thymus atrophy. Severe thymus atrophy should also be added to the signs of maternal toxicity on page 43, last paragraph. Page 22 table 11 /second part of the table: Headline of second column: to be changed from 'dose mg/kg body	It has been corrected. It has been added.	Noted Noted Noted

Date	Country/ Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		weight, mg /kg diet' to 'dose, ppm in the diet (mg/kg body weight)'.	It was changed to "dose, ppm in the drinking water or in the diet (mg/kg body weight)".	Noted
		For the drinking water study as well as for the dietary study reported in chapter 4.7 it should be indicated which type of formulation of DMTC (solid material or aqueous solution) has been used to create the finally administered test substance preparation.	There is no indication on the type of formulation of DMTC available in the study report.	Noted
		For both of the 13 week studies it should be indicated, whether or not reproductive organs have been evaluated during these studies. If the answer is yes, information should be provided on the nature of the investigations performed. In addition, even in case of negative results, these should be reported in the table.	There is no evaluation of the reproductive organs in both of the 13 weeks studies. This information has been added in table 11 on page 22.	Noted
		Page 30, table following table 12: This table includes the reporting of a 28-d repeat-dose toxicity study (BIBRA, 1998) on the chemical 2-ethylhexyl mercaptoacetate (CAS 7659-86-1). This study neither tested the substance relevant for this dossier (dimethyltin dichloride, CAS 753-73-1) nor is it a study on developmental toxicity. Reporting of the study BIBRA (1998) study should therefore be omitted.	Ok. The study of BIBRA has been deleted.	Noted
		As DMTC is reported to contain di/monomethyltin mixtures as impurities/constituents at proportions of approximately 50-90 % (by weight), also the available information on investigations on developmental neurotoxicity of monomethyltin, such as the studies of Noland et al. (1982) and Moser at al. (2006) should be considered in the dossier in chapter 4.11.2: Noland EA, Taylor DH, Bull RJ. Monomethyl and trimethyltin compounds induce learning deficiencies in young rats. Neurobehav Toxicol Teratol;	Given that the effects were greater with higher proportions of DMTC in the study of Rohm and Haas Co. (1999), it is concluded that DMTC is the more potent of the	The RAC agrees that there is no added value to add the MMTC studies.

Date	Country/ Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		1982; 4: 539–44. V.C. Moser, S. Barone Jr., P.M. Phillips, K.L. McDaniel, K.D. Ehman, Evaluation of developmental neurotoxicity of organotins via drinking water in rats: monomethyltin, Neurotoxicology 27 (2006) 409–420. Page 36, paragraph below end of table: Please clarify why a justification of read-across between DMT(EHMA) and DMTC is provided in chapter 4.11.2 as there are no studies taken into consideration using DMT(EHMA). Page 46, middle part "A classification Repr. 2 H361d" is proposed for DMTC (see separate CLH dossier)." Please clarify the bracket term. "Considering the rapid gastric hydrolysis of DMT(EHMA) into DMTC, a classification of "Repr. 2 H361d" is proposed for DMTC(…)." Please clarify the meaning of this sentence. Comment on classification proposal: Based on the presentation of the available data base in the dossier, the proposal to classify DMTC as Repr. 2; H361d is supported. However, there are some remarks to make: 1. The cleft palates observed at the highest dose (20 mg/kg bw/d) (Noda, 2001, first study) seem to be an incidental finding. Severe maternal toxicity (mortality, clinical signs of toxicity (e.g. tremor and convulsion)) occurred at the high dose; there is no dose-response	two components (DMTC and MMTC). Consequently, we consider having covered the worst case scenario. Therefore, there is no need to add the MMTC studies, as we prefer modifying our proposal as minimal as possible after the public consultation. It has been deleted. The bracket term has been deleted. This sentence has been deleted: it concerns DMT(EHMA) but not DMTC. Thanks for your support 1. Although, the cleft	Noted Noted Noted Noted The RAC supports classification for Repr. 2 (H361d). due to maternal toxicity and the contradictory neurotoxic effects.

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		relationship and no reproducibility. 2. It is difficult to evaluate the developmental neurotoxic potential. Adversity of the behavioural test findings should be discussed in more detail. The significant reduction in brain weight seems to be more relevant to classify for developmental toxicity. Since there is no dose-response relationship in brain weight reduction, classification for Repr. 2 – H361d is sufficient.	palates occurred with severe maternal toxicity, this is such a rare and severe malformation in rats that we consider it has to be taken into consideration. Besides, skeletal and visceral malformations are observed from the dose of 10 mg/kg bw and onward, which support the classification in Repr. 2. 2. Neurotoxic effects have already been presented in the proposal and taken into account in our proposal for classification.	
29/03/2012	Belgium/ MSCA	We support the classification proposal for reproductive toxicity as Repro.2 H361d for DMTC, based on induction of cleft palate in rat foetuses, reduced foetal weight and observation of a developmental neurotoxic potential. We agree that the evidence is however not considered sufficient (studies on only one species, absence of reproducibility in different studies, maternal toxicity) to place the substance in category 1B.	Thanks for your support	Noted
30/03/2012	Sweden / MSCA	We question the conclusion that the evidence is only sufficient to classify in Repro Cat 2. We think that it should be considered to classify in Repro Cat 1B based on the presence of cleft palate both at dose level 15 and 20 mg/kg/day (2.5 and 22.5 % respectively). Cleft palate was not detected in the second developmental study, however, this can be explained by the fact that the critical period for formation of the palate is around day 15.5 for rats. The three day dosing regime with dosing day 13–15 and day 16–17 could explain why no cleft palate was detected in the second study, either because concentrations high	Considering the maternal toxicity, the absence of reproducibility and absence of dose-response relationship, we think that classification in Repro. 2 is more adapted. The information on the period for formation of the	The RAC supports classification for Repr. 2 (H361d). due to maternal toxicity and the contradictory neurotoxic effects.

Date	Country/ Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		enough to cause damage in the fetus was not reached with only a three day dosing (not reaching high enough steady-state levels) or that dosing did not take place at the sensitive window of development. On page 33–36 the BIBRA (1998) 28 days study is placed in the table of studies for developmental toxicity – why?	palate around day 15.5 for rats is interesting, but we think that the periods of day 13-15 and day 16-17 are very close to the day 15.5 and cannot explain totally the absence of cleft palate formation. Bibra's study has been removed because it concerns DMT(EHMA) and not DMTC.	Noted
30/03/2012	Netherlands/ MSCA	The proposed classification for DMTC and DMT(EHMA) is Repr. Cat. 2 H361d and Repr. Cat 3, Xn R63) based on CLP and DSD, respectively. The substance is discussed in the TC C&L in 2006, and new information is presented by the dossier submitter. We want to share our doubts regarding the proposed classification. The main developmental effect (cleft palates) was observed only in the presence of (severe) maternal toxicity effects (20% mortality) and is therefore considered to be secondary to the maternal effects (CLP Annex I part 3.7.2.4.3). We agree that cleft palates are rare and serious malfomations. However, there is no knowledge on the occurrence of cleft palates in pups when the health of the dams is severely affected. The absence of cleft palates in the experiment with exposure during a limited interval of 2 days covering the same exposure window is a further indication that the effect may related to the maternal toxicity. It is acknowledged that DMTC can reach the foetal brains after administration to pregnant dams, and that brain weight reductions and histopathological lesions in the brain were shown in the developmental neurotoxicological study (exp. 1), although brain weight reductions were not decreased in a dose dependently way and the histopathological lesions are not statistically significantly different from controls. Moreover, these lesions were not reproduced in the second	Although cleft palate seems to appear with maternal toxicity, there are important skeletal and visceral malformations that occur at lower doses (5 and 10 mg/kg) without maternal toxicity and there are neurotoxic developmental effects. So we think that classification in Repr. 2 is adequate.	The RAC supports the arguments of the MSCA and the proposal for classification in Repr. Cat 2 (H361d).

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		experiment. The effects on the brain such as reduced brain weight could also be related to the lower pup body weight. Maternal effects, other than body weights and food consumption, were not reported in this study. The foetal effects were observed at levels above the LOAEL in repeated dose studies. Further, pups may also be directly exposed to the test substance in the lactation period. This makes it unclear whether there is a specific effect on development or just the same effect as observed in the adult animals. Based on the above we wonder whether the neuropathological findings in the foetuses can be considered developmental effects. Based on the presented information we propose not to classify the substance for developmental toxicity. Other organotin compounds Other organotin compounds such as dibutyltin have been classified as toxic to the development and others such as dioctyltin are under consideration for classification as toxic to the development. This is for dioctyltin based on positive results in other species. A read-across could be considered to strengthen the classification proposal for dimethyltin.	If read-across would have been included in the dossier, we think that it would be more appropriate to base a read across on MMTC (monomethyltin trichloride) classified Repro. 2 H360d, than on dibutyltin or dioctyltin. No read-across has been incorporated in the dossier, as the dossier concerns a hand-over substance: we therefore preferred to modify it minimally. Moreover, we think that there are sufficiently data to classify DMTC in Repro 2 H360d.	The RAC agrees with this MSCA conclusion.

Respiratory sensitisation – no comments received

Other hazards and endpoints

Date	Country/ Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
26/03/2012	Germany/ MSCA	Any other hazard classes or endpoints: Acute dermal toxicity, pages 4 (table 2), 9 (section 1.5), 18 (section 4.2.1.3), and 19 (section 4.2.4) Please consider changing the proposed DSD classification from Harmful (R21) to Toxic (R24). Justification: In the dossier, the dermal LD50 is given as 404 mg/kg bw. However only two of the applied three dose levels resulted in lethality. Moreover, 6/10, i. e. > 50 % of the animals died after having	The proposed classification in the CLP regulation corresponds to the acute tox 3 H311. Although Xn R21 had been adopted by ECB, we agree that data available are in agreement with T;	The RAC agrees with this decision due to lower LD50 in other studies.

Date	Country/ Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		received 400 mg/kg. Thus there is a high degree of uncertainty about the LD50 estimate of 404 mg/kg bw. This is confirmed when running the data through US EPA's BMD software: almost all of the available models result in a BMD50 slightly > 400 mg/kg bw, but the BMDL50 (95th percentile) is always clearly < 400 mg/kg bw. As 400 mg/kg bw marks the border to the next higher toxicity category under the DSD system, it would appear prudent to propose this higher category. Skin corrosion, pages 4 (table 2) and 29-30 (section 4.5): Please consider assigning CLP classification of "Skin Corr. Cat. 1" instead of "Skin Corr. Cat. 1B" Justification: This is the approach recommended by the ECHA Guidance on the Application of the CLP criteria" in cases where "[…] the data used for classification does not allow differentiation between the skin corrosion categories 1A/1B/1C . This situation appears to apply here, as neither of the two available studies evaluated skin reactions at exposure times =< 3 min as required for discretion between Cat. 1A and 1B. Based on the corrosive property and the classification for Acute Tox 2 – H330 (inhalation) it should be considered to include EUH071 - Corrosive to the respiratory tract. Repeated dose toxicity, pages 4 (table 2) and 22-29 (section 4.8) DE agrees with the proposed classification for DMTC with STOT RE1 – H372 with nervous system as main target organ, assuming that the effects are not based on acute toxicity. This aspect should be discussed in the dossier. Please consider discussing classification with STOT SE 3. Rational: It is noted that 24 notifiers to the CLP Inventory assigned a classification for STOT SE 3 (while apparently others did not), but this is not discussed in the dossier.	R24 classification in the DSD (although the BMDL50 is slightly above 400 mg/kg bw). So we agree to propose the classification T; R24 in the DSD. Skin corrosion appears after a four-hour exposure time (Rush, R.E. 1993b) at the 1-hour scoring interval. Indeed, classification proposal in catégorie 1B seems to be too much severe. However, ECHA has suggested us to detail exposure time and observation times to allow independent comparison with criteria. We agree with your comment and therefore have modified our proposal for Skin Corr 1C. If EUH071 is considered, STOT SE3 is not necessary as less severe than EUH071. I think we can adopt EUH071, based on the fact that the substance is classified as Skin Corr (page 22).	The RAC notes that the available information does not allow differentiation between the subcategories, classification in Skin Corr. 1 (H314) is proposed.

Date	Country/ Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
26/03/2012	Germany/ TIB Chemicals AG	Toxicokinetic data from human (accidents) and from animals (rat. mouse) show that dimethyl tin is methylated in vivo to trimethyl tin. Specific information see attachment *ECHA comment: The attachment document methyltin compounds V2.pdf is copied below. Attachment no. 1.* Acute toxicity of dimethyltin and human health An evaluation the CLH report "Proposal for Harmonised Classification and Labelling" for dimethyltin dichloride, DMTC form ANSES (on behalf of the French MSCA) we find data lacking on acute humantoxicity. In literature there are reports available, which are cause for increasing concern on this substance group. The acute toxicity of di- and trialkyltin compounds rapidly declines with the length of the alkyl chain, because mostly of their lower dermal and gastrointestinal absorption [8], [9]. Rey [1] reported the cases of six workers exposed to a mixture of dimethyl and trimethyltin (75:25) while cleaning a caldron. The reported exposures were a maximum of nine periods of ten minutes each on three consecutive working days. All workers wore the required personal protective equipment (prescribed protective clothing and gas masks) during all procedures. After a latent period of one to three days neurological deficits and systemic adverse effects were reported in these individuals. Apportion of the clinical report reads: "presence of associated neuropsychiatric symptoms, epileptic activity in the EEG, leukocytosis, serum transaminase […], need for artificial ventilation in three of the six patients. Several EEGs contained right sided frontotemporal delta-waves with acute stop intermissions in the temporal region which were compatible with dream attacks. Focal spiking in the temporal region was noted in one case, while the five others showed all rhythmic temporal discharge of delta waves." One of the six exposed individuals died twelve days after the initial	Although the neurological effects are well described in the Rey and Yoo studies, data on the doses are lacking, as it is often the case in epidemiologic studies. Besides, we wonder if the exposures of 9 periods of 10 minutes each on 3 consecutive days (Rey) and the four days exposure (Yoo) can be considered as an acute toxicity exposure. Indeed, according to the guidance on the application of the CLP criteria, "acute toxicity means those adverse effects occurring following (...) an inhalation exposure of 4 hours". Those studies are borderline between acute and repeated. We decided to consider these studies within the repeated toxicity studies, consequently, these adverse effects are taking into account by the STOT RE1 classification.	RAC agrees with this argumentation in that the STOT RE1 cover these effects.

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		exposure "with coma, respiratory depression, ARDS, shock, anuria and liver cell damage." An autopsy revealed massive degeneration of liver cells and necrosis, shock kidney and cerebral edema with irreversible damage of brain regions. Two other patients showed permanently neurological deficits (one of these is still a patient in a neurological hospital, last information from March 2012). The three other exposed individuals recovered to be clinically healthy, though a memory loss of six months was reported. Yoo [2] reported the case of a 43 year old man who cleaned a tank on four consecutive days. The tank previously contained dimethyltin dichloride (trimethyltin content approx 0.3%) The man wore personal protective gloves and had external air supplied via a mask. One day after finishing the job, he reportedly suffered from dizziness and disorientation; he had hallucinations, was irritable and had diminished memory. These behavioural changes did not improve and mental deterioration progressed over three post-exposure days. He was transferred to a hospital on day four after the last exposure. On the fourth day of hospital admission, the patient deteriorated into a state of coma and was placed on mechanical ventilation. He also showed metabolic acidosis in arterial blood gas analysis along with servehypokalemia, and difficulty in speriration [respiration?]. Electrocardiogram showed ST depression and T-wave flattening due to hypokalemia. The patient showed signs of acute renal failure on the following day. An analysis of the urine and the blood of the patient detected both dimethyl and trimethyltin. The ratiofor relative concentrations of DMT: TMT in the urine was approximately 1:2 and the ratio in the blood was 1:5. The patient was discharged from hospital on day 163, still showing moderate motor ataxia, memory loss and difficultly in speaking. A further case is reported by Giu-bin [3] and Jiang [4]. During 1999 New Year´s Day [in China?], more than 1000 people were poisoned by	We do not think that this study does modify the classification proposed by oral route. Therefore, and in order avoiding modifying the proposal too much after public	The RAC supports this conclusion of the MSCA.

Date	Country/ Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		organotin-contaminated lard. The analyses of the lard detected mainly dimethyltin-containing compounds. Hundreds of people were hospitalized and three people died. Giu-bin suggested that there may be a methylation of dimethyltin into trimethyltin. The cases reported by Yoo and Jiang provided some evidence of transformation of dimethyl to the more highly toxic trimethyltin in humans. Evidence to support this hypothesis was published by Furuhashi etal. [5] who showed, in an in-vivo experiment in mice and rats, that the methylation of dimethyltin to form trimethyltin species could occur in rodent species. The formation of trimethyltin from dimethyltinmay explains the neurotoxicity observed in patients exposed to the dimethyltin only. The studies of Yoo, Giu-bin and Jiang create at least a rebuttable suspicion that methylation occurs in the blood (higher concentrations, renal dialysis). The dimethyltin is distributed in and possibly metabolized in the blood through an interaction with hemoglobin [10]. The hemoglobin coordinated dimethyltin can exchange anions (e.g. Cl^-, CH_3^-) with thered blood cells [11], [12] and may interact with DNA [13], [14]. As trimethyltin the blood-brain-barrier will be passed and the well-known neurotoxic will be caused. An additional interesting point is the hypothesis of the similarity of the adverse effects and the toxicokinetics from trimethyl lead and trimethyltin compounds for instance discussed by Bondy [6] and Walsh [7]. This appears in a comparison from Florea [8] of potential toxic effects of different metals and their compounds. Sources: [1] Ch Rey, et al., Methyltin intoxication in six men: toxicologic and clinical aspects, Vet Hum Toxicol.1984 Apr;26(2):121-2) [2] Cheol In Yoo et al., A case of acute organotin poisoning, J Occuo Health, 2007, 49: 305-310	consultation, these data are not added in our proposal.	

Date	Country/ Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		[3] Gui-bin et al., Tin compounds and major trace metal elements in organotin poisoned patient's urine and blood measured by gas chromatography flame photometric detector and inductively coupled plasma mass spectrometry, Bull. Environ. Contam. Toxicol. 2000, 65: 277-284 [4] Jiang et al., Speciation analysis of organotin compounds in lard poisoning accident in Jiangxi Province, China, Science in China (B), 200, 43,5:531-539 [5] Furuhashi et al., Methylation of dimethyltin in mice and rats, Chem. Res. Toxicol., 2008, 21:467-471 [6] Bondy et al., The relation of the neurotoxicity of organic tin and lead compounds to neurotuble disaggregation, NeuroToxicology, 7, 1:51-56 [7] Walsh et al., Organometal-induced antinociception: A time- and dose-response comparison oftriehtyl and trimethyl lead and tin, Toxicology and Applied Pharmacology, 1984, 73, 295-299 [8] Florea et al., Occurrence, use and potential toxic effects of metals and metal compounds, BioMetals, 2006, 19: 419-427 [9] Barnes et al., Toxic properties of some dialkyl and trialkyl tin salts, Brit. J. Industr. Med, 1958,15:15-22 [10] Barbieri et al., A 119Sn Mössbauer spectroscopic study on the interaction of dimehtyltin (IV) derivates with rat hemoglobin, and of related model systems in aqueous solution, Journal of inorganic biochemistry 1988, 32:89-108 [11] Wieth et al., Organotin-mediated exchange diffusion of anions in human red cells, The journal of general physiology, 1979, 73:765-788 [12] Trabucco et al., Methylated tin toxicity a reappraisal using rodent models, Archives Italiennes de Biologie, 147: 141-153, 2009. [13] Nazari et al., Stability of DNA upon interaction with dimethyltin dichloride, Med Chem Res, 2007,16:238-257 [14] Dopp et al., The cyto- and genotoxicity of organotin compounds is dependent on the cellular uptake capability, Toxicology, 2007, 232(3):226-234 *End of attachment 1.*		

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON DIMETHYLTIN DICHLORIDE (DMTC)

Date	Country/ Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
30/03/2012	Sweden/ MSCA	Acute toxicity: The proposal of classification of DMTC for dermal acute toxic is unclear: in table 1.2 the proposal is Acute Tox 4, H312, however, in table 1.4 and in the comparison with criteria 4.2.4 the proposed classification is Acute Tox 3, H311. Please clarify. We support the proposal for Acute Tox 3, H311 since the LD50 value is >200 mg/kg bw and <1000 mg/kg bw. Skin sensitization: The proposal to classify DMTC as Skin Corr. 1B is based on the Rush study as the protocol of the AME study does not allow a direct comparison with the corrosion criteria. However, the description of the Rush study is somewhat confusing as it says in the table that the exposure period is 4 hours and that the responses were scored 1, 24, 48 and 72 hours after patch removal - it is not clear that the corrosive response appeared within 1 hour of application. Please clarify.	There was a mistake concerning the proposal "Acute Tox 4, H312". The classification proposed is "Acute Tox 3, H311". It has been corrected. It has been clarified. Skin corrosion appears after a four-hour exposure time (Rush, R.E. 1993b) at the 1-hour scoring interval. Indeed, classification proposal in catégorie 1B seems to be too much severe. So the most appropriate classification seems to be Skin Corr 1C,	Noted Noted The RAC proposes Skin Corr 1, because the available information does not allow differentiation between the sub-categories.

ATTACHMENTS RECEIVED:1

1. **methyltincompounds V2.pdf .** Submitted by Germany / Sven Hansen / TIB Chemicals AG. Attachment has been copied to the "Other Hazard and Endpoints "section of the table.