TIBCHEMICALS

TIB Chemicals AG | Mülheimer Straße 16-22 | 68219 Mannheim | Deutschland

European Chemical Agency
Annankatu 18

00120 Helsinki
Finnland

E-Mail | Email
Sven.hansen@tib-chemicals.com

Telefon | Phone
+49 621 8901-406

Fax | Fax

Datum | Date
01 Dec 2017

In the CLH Proposal from KEMI, dated July, 7th, 2017 concerning

EC# 222-883-3
Name: Stannane, bis(lauroyloxy)dioctyl-

and

EC# 293-901-5
Name: Stannane, dioctyl-, bis(coco acyloxy) derivs.

The proposed classification of the named substance(s) (in the following named DOTL) is

Repr. 1B
STOT RE 1.

The justification of the proposed harmonized classification in the CLH-Report is based on a grouping approach and read across to Dioctyltin dichloride (DOTC).

The Swedish Competent Authority correctly explained the background of using read across in the light of newer simulated gastric hydrolysis studies, which showed that Dialkytin mercaptoacetates do not form Dialkyltin dichlorides but remain at the stage of a monocloroester of the respective dialkyltin substances.

In their hypothesis for the analogue approach for DOTL the Swedish Competent Authority considered that grouping of organotins needs to take into account “in greater detail the nature of labile ligands and the chemistry associated to the relevant organotin substances”.

So the hypothesis for the analogue approach is that “following, both the source and target substance will hydrolyze with the generation of common intermediates. Systemic exposure will therefore be to the same substance(s) regardless of the substance administered”.

In the CLH report two studies are cited on the hydrolytical behavior at low pH of DOTC (potential source substance) and DOTL (potential target substance) (Naßhan 2015 and 2016).

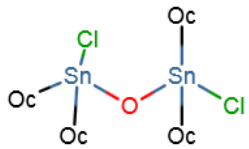
The DOTC study shows that DOTC hydrolyzed under the conditions of the study (HCl, pH 1.2, 4h 37 °C) to a dimeric form of 1,1-dichloro-1,1,3,3-teraoctyl distannoxane (see figure 2). After 4 hours 90 % of the distannoxane has been formed besides 10 % unreacted DOTC. The substances have been characterized by 119-Sn-NMR-specroscopy. The signals characteristic for the distannoxane appear as two sharp singlets at -92 ppm and -145 ppm.

The DOTL hydrolysis under the same conditions resulted in a complex mixture of tin containing substances. The two characteristic singlets at the same chemical shift could be assigned to approx.- 16 % formation of the described distannoxane.

So, hydrolyzates of DOTC and DOTL formed under the same conditions may have some similarities.

The NMR-spectrum of the distannoxane shows two singlets. This is not to explain by a monomeric structure of the molecules since both tin atoms in this structure would be symmetrically substituted resulting in only one NMR-signal.

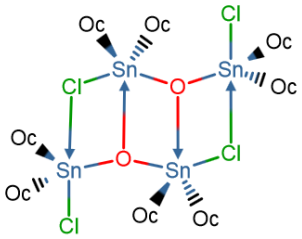
Figure 1 – Structure of monomeric Distannoxane



The chemical shift of the two different tin atoms are in a range which is typical for a five fold coordination of the tin atom.

These results clearly prove a dimeric ladder structure of the distannoxane

Figure 2 – Ladder structure of dimeric Distannoxane



This dimeric ladder structure is described in literature e.g. Harris, R.K., Sebalt A., Journal of Organometallic Chemistry, 331, (1987) C9-C12 for further literature see annex literature).

It has been characterized by X-ray analysis for a great number of derivatives.

Recent MS studies (Letzel 2017) using different Ionisation techniques (ESI, MALDI-TOF, LIFT) are consistent with the literature and the NMR-results.

In the studies both DOTC and DOTL have been hydrolyzed under the same conditions, the products extracted and analyzed.

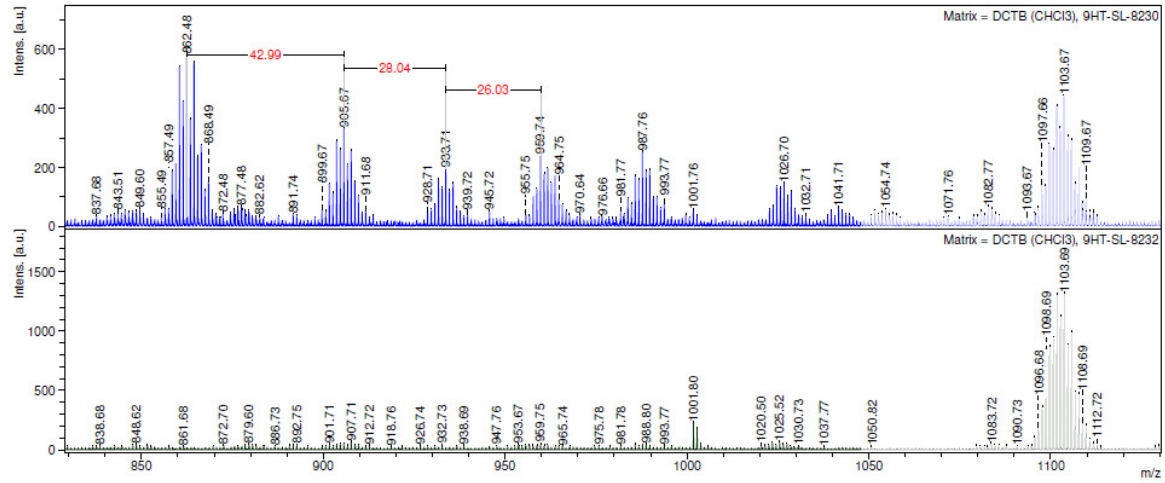
In both spectra high molecular masses and their further fragmentation can be detected. The DOTL spectra contain besides the dimeric stannoxane further signals for fragments associated with the fatty acid.

Figure 2 – Fragmentation MALDI-TOF measurement (blue: DOTL, black: DOTC)

Analysis Info

Analysis Name	EXT 20171128\0_N23\1
Comment	Matrix = DCTB (CHCl3), 9HT-SL-8230
Acquisition method name	D:\Methods\flexControlMethods\RP_400-4000x_Da.par
Number of shots	3500
Position	N23
MSMS parent mass	
positive voltage polarity	POS

Operator	MLE
Acquisition Date	2017-11-28T12:39:39.000



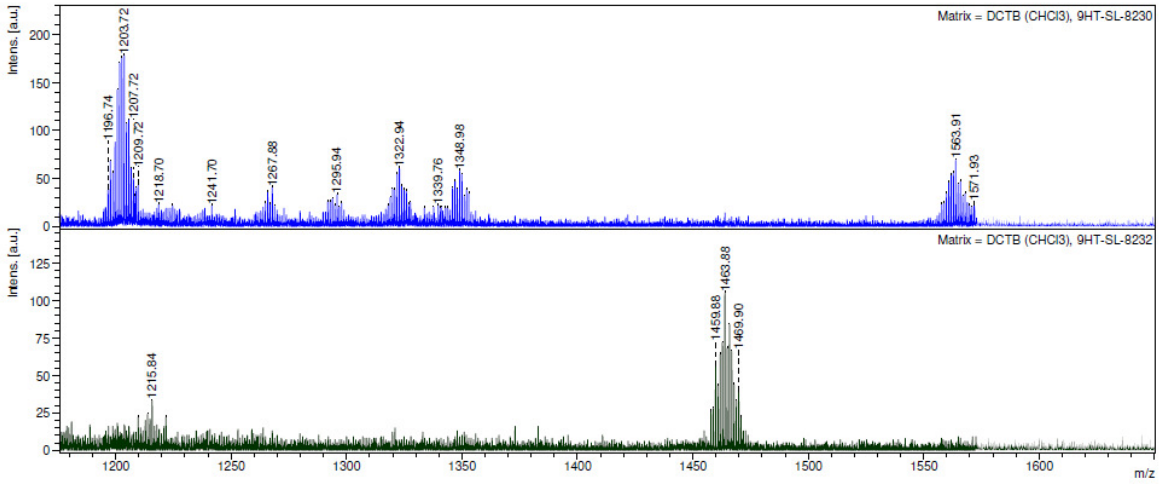


Figure 5 – Fragmentation of DOTL hydrolysis products in ESI mass spectroscopy

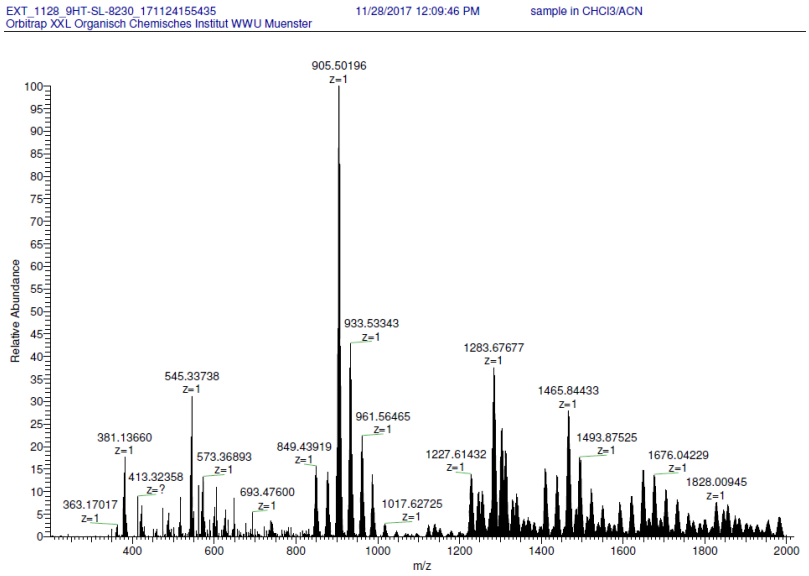
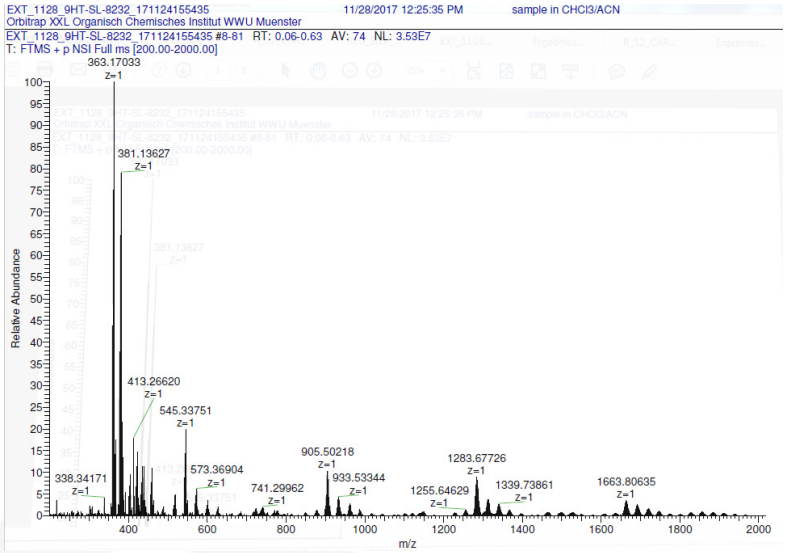


Figure 6 – Fragmentation of DOTL hydrolysis products in ESI mass spectroscopy



Conclusion:

The cited 119Sn- NMR based studies and the recently conducted MS-based studies together supported by literature unequivocally show that the hydrolysis product 1,3-dichloro-,1,1,3,3-tetraoctyldistannoxane exists in a dimeric form (Figure 2)

The molecular weight of this molecule is 1554 Da, which is far beyond the molecular weight which can pass a biological membrane.

So even if formed by both substances (source and target) under low pH conditions this substance cannot pass the membranes of the gastrointestinal tract and thus is toxicological not of relevance.

Therefore, the effects found in animal studies on DOTC must not be attributed to the dimeric distannoxane. They are likely to be attributed to the remaining DOTC present in the DOTC hydrolyzate. Consequently, reading across from DOTC feeding studies to DOTL is not appropriate, since no DOTC was detected in the DOTL hydrolyzate.

Similarly, a harmonized classification on this substance based on scientific facts cannot be done based on read across from DOTC.

Generating new data on the substance itself seems to be the only way to accurately characterize the reprotoxic potential and specific organ toxicity of DOTL and adequately address uncertainty of the substance classification.

Annex literature Distannoxane:

1) R. Harris and A. Sebald, J. Organomet. Chem., 331 (1987) C9-C12
2) T. Yano, K. Nakashima, J. Otera and R. Okawara, Organometallics 4 (1984) 1501
3) H. Puff, E. Friedrichs and F. Visel, Z. Annorg. Allg. Chem., 477 (1981) 50
4) J.F. Vollano, R.O. Day and R.R. Holmes Organometallics, 3 (1984) 745
5) H. Puff, I. Bung, E. Friedrichs and A. Jansen, J. Organomet. Chem., 254 (1983) 23
6) H. Puff, W. Schuh, R. Siever and R. Zimmer, Angew. Chemie Int. Ed. Engl. 20 (1981) 591
7) P.G. Harrison, M.j. Begeley and K.C. Molloy, J. Organomet. Chem., 186 (1980) 213