Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Dioctyltin bis(2-ethylhexyl mercaptoacetate)

EC number: 239-622-4
CAS number: 15571-58-1

ECHA/RAC/CLH-O-0000002543-78-01/A2

Adopted

8 June 2012

ANNEX 2.1: COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

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

Substance name: Dioctyltin bis(2-ethylhexyl mercaptoacetate)
EC number: 239-622-4
CAS number: 15571-58-1

General comments

Date	Country / Person / Organisation / MSCA	Comment	DS response to comment	RAC response to comment
03/05/2011	Germany/ Matthias Plog / Member State	The proposal for harmonised classification and labelling of dioctyltin bis (2-ethylhexyl mercaptoacetate) including the scientific justification (page 6, 2.2) can only be checked for plausibility. The proposed classification and labelling of dioctyltin bis (2-ethylhexyl mercaptoacetate) as Repro Cat 3 R63 (DSD), respectively Repro Cat 2 H361d (CLP) is not supported (for details see below). Plausibility check also only applies for the reported study results in the submitted dossier, in particular the studies concerning reproductive toxicity and development, since none of the study reports (except one reference) has been published so far. Consequently one has to rely on the reporting and interpretation of the study results of the dossier submitter. The dossier and its comprehensibility should be improved and substantiated, in particular for the key studies related to reproductive toxicity and developmental toxicity (the same applies for the RDT studies as far as data on the reproductive organ system were collected during these studies). Reporting of more details on (i) the study design (e.g. animal numbers/dose groups, etc.) and on (ii) the study results (such as	The CLH dossier has been reworked and now contains additional details; Some of our response hereafter may imply further input and discussion with the authorities to explain more substantially the classification proposal made by Industry. The reports are available if you need further information. The report of the two generation study (LTP, 1997) is only partly available (the individual and mean summary tables are not provided by the owner of the study (still waiting for the full report). There were no analysis of estrous cycle and sperm in the 2-generaton study. However, the microscopic examination of the testes and ovaries have	Additional data has been added, even though the comprehen s-ability could have been improved even further. However, the database is sufficiently solid to conclude on the need for classificatio n for reproductiv

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		data from the (histopathological) evaluations of organs from the reproductive system, data on body weights, data on litter sizes, implantations, resorptions etc.) are necessary. As the two-generation reproduction toxicity study was conducted at LTP Hamburg in 1997, it is assumed that no data on spermatology and oestrous cyclicity are available, which is considered a limitation in the data base. Further, it appears that the reproduction/developmental toxicity screening study was not a stand-alone study but rather combined with a preceding subchronic toxicity study, from which information on the performance of the male/female reproductive organ system should be available. Overall, the studies considered relevant for the classification proposal should be reported in more detail. Minor, editorial comments: Page 34, 5th para, brackets: 6.8 -6.8 mg/kg bw/d ?? Page 34, last line, brackets: equivalent to 0.77 mg Sn/kg bw/d for comparison, what amount of daily Sn intake are the applied dosages in all the other studies equivalent to ?? Page 35 1st line: .. mice developmental rabbits study ?? Page 35 last para: groups 2, 3 and 4 are not explained. Was the percentage of implantations really as poor as reported in the dossier?? If so, the validity of the whole study has to be questioned. Page 36, 2nd & 7th para: the conclusions of the authors (slight embryolethal and moderate retardive effects) can not be comprehended and agreed without any further detailed information on the results of this study. Page 38: it is not clear, whether the study of Appel and Waalkens-Berendsen (in the dossier sometimes spelled as Apple) are two different studies. Report page 4, chapter 1.1 substance:	reported no effect. In addition, the combined reproduction/developmental toxicity screening study has reported no effect on sexual organs. Text amended. Page 35. It is post-implantation loss and not the number of implantation. Corrected. Page 38: same study. corrected DOT(2-EMH) is considered as a mono-constituent in this dossier. The wording is modified.	e toxicity. Noted.

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		According to REACH substance definition (RIP 3.10), it is not correct to say that DOT(2-EMH) is manufactured as a mixture with DOT(2-EMH). In fact, the described substance seems to be either a mono-constituent or a multi-constituent substance. In line with the substance identity described in Part A chapter 1.1, MOT(2-EHMA) is an impurity of the substance DOT(2-EMH). As „mixture" is the wrong term in the present case the description should be adapted. Report page 10, chapter 1.2 Composition of the substance: As already stated for Part A of the dossier, it is not correct to say that DOT(2-EMH) is manufactured as a mixture with DOT(2-EMH). In fact, the described substance seems to be either a mono-constituent or a multi-constituent substance. These terms should be used to explain the approach made in the dossier.		
06/05/2011	Sweden / Member State	Identity of the substance (part B, Chapter 1) Many different substance names are used in the dossier without being fully explained (DOTC, DOTE, DOT (IOTG), dioctyltin bis(IOMA)/octyltin tris(IOMA), dichlorodioctylstannane), and a listing and explanation of all substances in this chapter is needed. The relationships between different substances (hydrolysis product, isomers, etc) are explained at different places in the document, but it would be beneficial to have all that information in this chapter. Because read across is used, the justification for the read across could also be explained in more detail in this chapter, clearly listing the substances for which the read across is felt justified. Very limited physico-chemical data are reported in chapter 1.3, based on the argument that the substance decomposes in water making testing difficult. However, in chapter 2.1 it is stated that the substance is produced in a water solution, which makes the decomposition argument difficult to understand. It would be helpful to get this aspect explained in more detail, and/or to get more data on the physic-chemical properties.	A listing and an explanation of the relationship between the different substances is added. The justification of read across is detailed under chapter 4. The substance does undergo rapid hydrolysis in water. However, the production is done in presence of water as a separate reaction phase with the product being in the organic phase. The aqueous phase is saturated with sodium chloride during the reaction, allowing an efficient phase separation. Due to these elements, the hydrolysis can be	The clarifications are very useful. The clarification is appreciated.

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			minimal although it takes place to some extent (hydrolysis products contained in the aqueous phase). More details are provided in the SIAR presented in SIAM 23.	
06/05/2011	France / Member State	We wonder why the information on the endpoints "oral and dermal acute toxicity", "skin and eye irritation", "skin sensitisation" and "mutagenicity" are presented in the CLH report, since they are not informative for the classification proposed in reprotoxicity. Information on repeated toxicity was also presented and shows that DOT(EHMA) caused the decrease in the absolute and relative thymus weights at all dose-levels in the second subchronic study (Anonymous, 1974), which was correlated with histopathological effects observed at 100 ppm (=1.6 mg/kg diet). This dose level is below the concentration limit of 10 mg/kg/day given in the CLP, and the classification STOT RE1 is well adapted. We consider that it would be necessary to harmonize the endpoint "STOT RE cat. 1" on the basis of the discrepancies of classification between the notifiers, as seen in the classification and labelling inventory report.	The others toxicological endpoints have been added in order to present an overview of the toxicological profile of the substance. Indeed, the data presented indicate that the substance can be classified as STOT RE cat.1. This classification is even included in the REACH registration dossier (self classification). However, according to article 36(3) & 37, industry is not likely to judge the need of an action at community level for this subject and lets Member States to decide it.	The toxicological profile is noted. The discussion is noted. Further activities on this substance is apparently dependent on MS initiatives.
09/05/2011	Belgium / Frédéric Denauw / Member State	Editorial comments: On p.6: one braket is at a wrong place leading to a confusing sentence ; First §: "A 2-generation study (…) was performed using mixture of DOT(isooctylthioglycolate)(CAS No…)/Octyltin tris (IOMA)(CAS No)) (78.8:16.9% mixture)." On p.6, 3rd §: the 2-generation study is from 1997, and not from 1992	Text amended accordingly.	Noted.

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		(anonymous, 1997) On p.10, we can presume that DOTE is another abbreviation for the substance DOT(2-EHMA). 2nd §: there is a mistake in the substance name: "Regarding the substance identity, dioctyltin bis(2-ethylhexyl mercaptoacetate) will be…" In Table 7, there is a mistake in the following name: "Mono-n-octyltin tris(2-ethylhexyl mercaptoacetate). In table 7, it would be useful to report in the column remarks for the dichlorodioctylstannane that there is a harmonized classification for this compound: Acute tox 3 *, STOT RE 1, Aquatic Chronic 3. (In 2003, not enough data were available to conclude on a classification for the reproduction. A screening test (OECD421) was proposed, which is now available. The harmonized classification for DOTC should be revised.) On p.13, the "In vitro gastric hydrolysis study" of Yoder is from 2003 (and not 2000), following the references. On p.14, 1st §, there is a mistake in "genotoxoxicity". On p.16, (4.2.3) DOTE is used instead of DOT: "DOTE(EHMA)". We would suggest to use the same abbreviation across the dossier for clarity, for instance "DOT(2-EHMA)". Same remark on p.18, 19, 22 and 26 (2x). On p.25: The study (Appel and Waalkens, 2004) was performed with Dioctyltindichloride which is DOTC, and not the hydrolysis product of DOTC (last but one §). On p.34 (1st §), for the F1 generation, reduction in relative thymus weight at 60 ppm is only reported for females on p.33. On p.34 (last §) and p.35 (2x), DOT(IOMA) and MOT(IOMA) are called here DOT(IOTG) and MOT(IOTG). A same abbreviation across the dossier could be suggested.	A listing and an explanation of the relationship between the different substances is added. The justification of read across is detailed under chapter 4 As DOTC is already in annexe VI, it is up to member states to propose a modification of an existing entry	The clarifications are very useful. Noted. . Further C&L activities on DOTC is dependent on MS initiatives.
09/05/2011	United Kingdom / Member State	For this substance, only the information relevant to the hazard class you are proposing to harmonise should be included in the CLH report. You should consider removing the information for other hazard classes not relevant for the classification of DOT (2-EHMA) as a reproductive	The others toxicological endpoints have been added in order to present an overview of the toxicological profile of the	The toxicological profile is noted.

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		toxicant. To avoid confusion, please ensure that a consistent approach is taken when referring to the isomers and hydrolysis products of DOT (2-EHMA). For example, Dioctyltin dichloride is referred to as both dioctyltin dichloride and DOTC interchangeably through out the report. Page 10- Dichlorodioctylstannane has an entry in Annex VI of CLP. We suggest that you provide this entry below Table 7 for clarity. It would be useful if the scientific justification in section 2.2 was presented more clearly. For example, insert an opening paragraph explaining that the proposal is based on the read-across of data from the similar substance DOT(IOMA) and the hydrolysis product DOTC and why this is appropriate. It could then go on to summarise the available information etc.	substance. A listing and an explanation of the relationship between the different substances is added. The justification of read across is detailed under chapter 4. The entry for dichlodioctylstannane is added. A clearer discussion of the chemistry and read across is provided in the revised CLH report.	The clarifications are very useful.

Carcinogenicity

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		No comments received.		

Mutagenicity

Date	Country/ Person/ Organisation/ MSCA	Comment	DS response to comment	RAC response to comment
		No comments received.		

Toxicity to reproduction

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03/05/2011	Germany/ Matthias Plog / Member State	The proposed classification as Repro. Cat 3 R63 respectively Repro. Cat.2 H361d is NOT supported. A classification as Repro. Tox. 1b H360FD is needed. Page 31, 4.11.2.1: We recommend adding to the prenatal developmental toxicity studies available data indicating a developmental immunotoxicity hazard from read-across with dichlorodioctylstannane. Developmentally toxic effects such as developmental immunotoxicity of dioctyltin compounds should be addressed in the dossier and therefore the following study should be included: Smialowicz et al. (1988) Immunologic effects of perinatal exposure of rats to dioctyltin dichloride, J Toxicol Env Health, Part A, (25) 4, 403ff) Page 34, Summary for effects on fertility: From the presentation of the two generation study in this paragraph it appears as if no effects related to possible fertility impairment were observed at all. However, on page 37, 1st para, it is reported, that a decreased number of pups per litter was seen in this study. Not any data on this endpoint, however, are presented in the dossier and thus there is a need for clarification – and for discussion, whether or not effects indicative for fertility impairment were seen during this study. Obviously there were effects seen on the postnatal development of the F0 as well as the F1 offspring at the high dietary concentration (increase in mortality, respectively decrease in viability and probably growth retardation during the lactational period) Furthermore, obviously signs of developmental immunotoxicity were revealed during this study, at least such effects are reported in the dossier (e.g. a decrease in relative thymus weight in male and female	The reference and summary are added in the dossier. More details are added in the text. Summary and individual tables are missing in the 2-genraration report, therefore no value on the decreased number of pups can be provided, however, the viability and lactation indices are relevant	The study has been added, but a more detailed description of the data had been needed. More data has been added, but still more details from the studies would have been useful.

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		weanlings at 60 ppm is reported on page 34, 9th para and in table 20). These effects observed on (postnatal) development during the two generation study should also be considered on page 36, summary for developmental toxicity, and on page 37 (4.11.5 and 4.11.6). Page 34, Summary for effects on fertility: From the reproduction/developmental toxicity screening study a dose-related reduction of the gestation index (71 and 50 % at 100, resp. 300 ppm) and a dose related reduction in live birth index (53 and 60 % at 100, resp. 300 ppm) indicative for fertility impairment is reported in the section above (however, also without any data on litter sizes and on implantations).The summary paragraph however, gives the impression, as if no effects indicative for fertility impairment were seen during this study. Also for the two-generation study under 4.11.5 it is mentioned that a decrease in number of pups per litter was observed. So it appears from the two mating studies with rats that besides postnatal development **also reproductive capability and capacity was affected**. Therefore, relevance of these latter effects for classification and labelling for fertility impairment needs to be discussed. This is all the more necessary, since the effects on fertility observed in the reproduction/developmental toxicity screening study at 100 ppm would not necessarily be explained by thymus organ toxicity and/or other types of systemic toxicity. Based on the database as presented in the dossier, we do not agree that dioctyltin bis (2-ethylhexyl mercaptoacetate) is devoid of adverse effects on fertility and would not need any classification and labelling for hazards related to fertility. **Rather we propose to consider the need for classification and labelling as Cat. 1B H360F.**	indicators of pups mortality. The proposal to consider a need for an additional classification as cat 1 B for fertility should be more discussed, Indeed, the two fertility studies (OECD 421 and the 2-generation study) are NOT reporting effects on the reproduction organs, no effects were observed on sexual organ weights or on the sexual behaviour, there was no effect on mating. The precoital time was comparable for the control and the treated groups, the female fecundity index , male and female fertility indices were not affected	The substance is clearly toxic to reproduction. However, based on the available data, it appears that all the toxic effects occur post-implantation, and therefore not a sufficient basis for classification for adverse effects on fertility.

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			while the gestation index was 86, 100, 71 and 50% in the control, 10, 100 and 300 mg/kg/groups, respectively which correspond to an effect on concepti development rather that a fertility effect.	
		Page 36, Summary for effects on developmental toxicity: The potential for developmental immunotoxicity (see above) should be included and addressed here. The developmental effects as observed in the two generation study (decrease in relative thymus weight in male and female weanlings at 60 ppm indicative for developmental immunotoxicity, pup lethality and impairment of postnatal viability, reductions in F2 pup body weights indicative of postnatal growth retardation, increase in stillborns for the F2 pups) and the reproduction/developmental toxicity screening study (postimplantation loss and reduced live birth index- indicative for embryo-/fetolethality, pup lethality and impairment of postnatal viability, runts – indicative for developmental retardation) should be summarised and included here. As to the three studies on prenatal developmental toxicity: prenatal death - fetolethality - was observed in the study with rats at marginally if at all maternally toxic dose levels; prenatal death – fetolethality - was also observed in the study on rabbits during which in addition induction of structural (in particular visceral) anomalies as well as distinct growth retardation (incomplete skeletal ossification and reduced fetal body weights) was revealed - **all at non-maternally toxic dose levels**. In the study on mice an increase in resorptions – embryolethality – was observed as well as the induction of external malformations (cleft palate, exencephaly, bent forelimbs) and skeletal anomalies at exposure levels without significant maternally toxic side effects except affections of	Text modified. It is important to highlight that the developmental effects were observed only in rabbits and mice (not in rats where it was only one rat female reported with dead fetuses). Indeed, no	RAC agrees with the comments that developmental immunotoxicity is indeed an issue to discuss in the report, and notes that this topic has not really been covered by the DS. RAC does not agree with the DS, but rather finds evidence of

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		thymus organ weight. Thus, from the data presented in the dossier there is unequivocal evidence for prenatal developmental toxicity from several independent studies in various species, postnatal developmental toxicity in rats as well as developmental immunotoxicity in rats. The pre- and postnatal developmental effects were observed at dose levels without systemically toxic side effects except effects on the thymus. However, there is no indication for the developmentally toxic effects to result from parental/maternal thymus toxicity and thus to represent secondary effects. Based on the database as presented in the dossier, we do not agree that dioctyltin bis (2-ethylhexyl mercaptoacetate) should be classified as Repro Cat 3, R63 (DSD), respectively Repro Cat 2 H361d (CLP) only. Rather we propose to consider the need for classification and labelling as Repro Cat 2, R61, respectively Repro Cat 1B H360D, since observed adverse effects on development are not considered to be a non-specific consequence of thymic toxicity and since there are not any deficiencies in the available studies making the quality of the evidence for developmental toxicity less convincing.	maternal toxicity were recorded in rats except for a marginal effect in one dam. Furthermore, rats did not show any of the abnormalities of bone formation seen in mice and rabbits. These developmental effects were always associated with maternal toxicity substantiated by decrease in thymus weight in the mice and abortion in the rabbits. Therefore, there is no clear evidence of an adverse developmental effect in the absence of maternal toxicity and there is no clear evidence that the developmental effects are	developmental toxicity in all 3 species studied. RAC also finds it highly unlikely that the maternal thymotoxicity can explain the observed toxic effects. Thus, there is ample evidence of developmental toxicity from 3 different species, with effects including post-implantation loss, fetotoxicity, resorptions, abortions, malformations, and developmental immunotoxicity. The clear

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		Page 37, (4.11.5 Comparison with criteria): The two separate endpoints –fertility and developmental toxicity – need to be considered and discussed each separately in the dossier. The discussion of endpoint related effects and their relevance for classification should take into account the according criteria for each of the two endpoints as provided in the CLP regulation. The discussion should clearly set out, why observed effects are relevant for classification and labelling or not relevant. It is recommended that after revision of the dossier chapters 4.11.1 – 4.11.6 also chapter 2 should be updated.	secondary to thymus toxicity. It is well-known that the rabbits and the mice are quite sensitive species for the assessment of maternal and developmental toxicity. The thymotoxicity especially during pregnancy may have exacerbated the developmental observed effects in both species. Text modified.	effects occur in the absence of marked maternal toxicity, and are therefore a basis for classification and labelling with Repro Cat 1B H360D (CLP). The comparison with the criteria is not sufficiently detailed in the report.
06/05/2011	Sweden / Member State	The reproductive toxicity studies are performed using dioctyltin bis(IOMA)/octyltin tris(IOMA) or dichlorodioctylstannane (=DOTC). The read across approach seem justified for DOTC, and based on the assumption that the read across from the other substances also are justified, it is clear that dioctyltin bis(2-ethylhexylmercaptoacetate) is affecting the reproductive development. However, we do not agree with the proposed classification (Cat 2 CLP / Cat 3, SDS). The criteria say that Cat 1B, H360 (CLP) should be assigned when there are "clear evidence of an adverse effect on development", which is the case for this substance. Adverse effects are reported from 3 different species, and include; ☐ stillbirths, pup mortality and delayed development in rats (Anonymous, 1997),	A group classification would make sense ONLY if the substance has been shown to undergo hydrolysis to DOTC under gastric hydrolysis and these data are missing for many	Noted

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		☐ post implantation losses and decreases in gestation, live birth and viability indices in rats (Appel and Waalkens-Berendsen, 2004) ☐ abortions , post implantation losses, skeletal variations, and reduced pup body weights in rabbits (Battenfeld, 1992), and ☐ resorptions and serious malformations (eg. cleft palates) in mice (Faqi, 2001). Thus, dioctyltin bis(2-ethylhexylmercaptoacetate) should be classified with Cat 1B D, H360 (CLP) and Cat 2, R61 (DSD). However, based on the read across arguments, it would make sense to create a group classification for all the substances that belong to this group (e.g., with DOTC as the common denominator), and not only classify one of them.	dioctyltin compounds. For DOTC, as it is an harmonized entry so its modification can only be on the initiative of a member state	Noted.
06/05/2011	France / Member State	The following need for clarification has been noted: • In the two generation study, the effects on the thymus weight are observed only in females at 60 ppm in the F1 generation according to the study description but in the summary of effects on fertility, it is specified that the effects on the thymus are observed on males and females, until weaning and on males during post-lactation. There is a discrepancy between the two versions. • Overall, there is confusion in the units used: between the "ppm" and the "mg/kg" and the "mg/kd diet" and in particular in the reprotox screening assay. • In the mice developmental study, it is not "the mice developmental rabbits study" but "the mice developmental study". • As regards to the maternal toxicity, can you please specify, in the developmental toxicity study in rats (p.34) what a marginal maternal toxicity is? Overall, (p.36) the main symptom of maternal toxicity is thymic atrophy, and is observed in the rat two generation study and in the mice developmental study but not in the rabbits. Indeed, the rabbit maternal toxicity is described as being the high incidence of abortion, but no other toxic effects are reported in the dams and it is not clear whether abortion is a sign of dams toxicity or a sign of reproductive toxicity. However, the rabbit embryotoxicity study shows serious skeletal malformations and visceral anomalies.	Text modified.	There are signs of maternal immunotoxicity in rats and mice, but as there is no plausible link between this effect and the different types of developmental effects, RAC is of the opinion that the maternal immunotoxicity has no

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		Significant increase in the incidence of cleft palate and bent forelimbs, significant exencephaly, skeletal variations (unossified digit, supernumerary cervical ribs, hindpaw incompletely ossified...) and skeletal abnormalities (bent vertebral column...) are observed in mice with maternal toxicity being limited to thymic atrophy. It is not clear how such developmental effects can be secondary to thymic atrophy and therefore to maternal toxicity. Besides, On the contrary, the rats do not exhibit skeletal malformations although the maternal toxicity on the thymus is observed in the two generation study. So, no clear link can be established between the maternal toxicity on the thymus and the foetal toxicity. Indeed, based on the CLP regulation, in the section 3.7.2.3.5 of the reproductive toxicity, we can read: " Generally, the presence of maternal toxicity shall not be used to negate findings of embryo/foetal effects."; and in the section 3.7.2.4.2 of the maternal toxicity paragraph: " Developmental effects which occur even in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be unequivocally demonstrated on a case-by-case basis that the developmental effects are secondary to maternal toxicity." The developmental toxicity effects such as cleft palate, exencephaly, visceral anomalies and serious skeletal malformations are observed in mice and rabbits and these effects must be taken into account, in accordance with the CLP regulation, section 3.7.2.4.2: "Moreover, classification shall be considered where there is a significant toxic effect in the offspring, e.g. irreversible effects such as structural malformations, embryo/foetal lethality, significant post-natal functional deficiencies." Besides, no information is available that could question the relevance of the effects for humans. Considering these strong effects on the foetuses (skeletal malformations) and that these effects cannot be considered secondary to maternal toxicity, we support the classification in category 1B of the developmental toxicity.		bearing on the reproductive toxicity observed in these species. No signs of maternal toxicity were noted in rabbits, and RAC therefore view the abortions as signs of reproductive toxicity rather than of maternal toxicity. RAC supports the notion that the data better fits the criteria for repro Cat 1B rather than cat 2.
06/05/2011	Ireland / Health and Safety Authority	The Irish CA does not agree with the proposed classification of Repr. Cat 2 H361d. In our opinion, the weight of evidence obtained from studies performed according to OECD Guideline 414 (Battenfeld 1991, 1992 and Faqi, 2001) and OECD Guideline 421 (Appel 2004) gives a clear indication of developmental toxicity and embryotoxicity of the	Text modified and requested information is added.	RAC supports the notion that the data better fits the

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		surrogate test substance in three different species which supports a classification of Repr 1B H360D. The dossier submitter proposes that the effects observed are mitigated by maternal toxicity. However, in our opinion, insufficient details regarding the incidence and severity of the maternal effects have been presented to allow an assessment of the influence of maternal toxicity on the effects observed. In the CLH proposal the maternal toxicity was described as "very slight". Section 3.7.2.2.1.2 of the Guidance on the Application of CLP criteria states: "…However parental toxicity that is less than marked should not influence the classification for reproductive toxicity independent of the specific parental effects observed". Therefore, we consider that "very slight" maternal toxicity is not a sufficient justification for not classifying the substance in a higher category and therefore we consider a classification of Repr. 1B H360D is more appropriate.		criteria for repro Cat 1B rather than Cat 2.
09/05/2011	Belgium / Frédéric Denauw / Member State	Toxicity for reproduction of DOT(2-EHMA) is assessed based on studies on the isomer DOT(IOMA) and on a study on the hydrolysis product of the substance (DOTC). We consider these studies as appropriate to assess the effects on reproduction of DOT(2-EHMA) for the following reasons: - DOT(2-EHMA) and DOT(IOMA) are isomers of the same compounds. They can be considered as chemically equivalent. - DOTC is the hydrolysis product of DOT(2-EHMA). DOT(2-EHMA) was demonstrated to be readily hydrolysed to DOTC under physiological conditions (101% hydrolysis within 30 minutes) (Yoder, 2003). Mammalian developmental effects of DOTC, by oral administration, can therefore be extrapolated to the parent compound DOT(2-EHMA). - DOT(IOMA) and DOTC show thymotoxicity. Two old supporting subchronic studies with DOT(2-EHMA) show also clear effects on the thymus (Anonymous, 1974 and 1970). A toxicological equivalence of the 3 substances can therefore be assumed. - A same approach is followed in the OECD SIDS for Dimethyltins (SIDS Initial Assessment Report for SIAM 23, Dimethyltin dichloride and selected thioesters, OECD, 2006) : The Dimethyltin dichloride (DMTC) and the 2 selected thioesters, namely DMT(2-EHMA) and DMT(IOMA) are considered one category of compounds for mammalian studies via the oral route, based on structural similarities and the demonstrated rapid hydrolysis of all of the esters to the DMTC. In addition, the breakdown products of DMT(2-EHMA) and DMT(IOMA) are the thioglycolate esters (2-EHMA and IOMA), which have	In the Battenfeld study performed in rats (1991) only one single dam was affected and presented a decrease body weight (-58g) at the high dose-level, it is the one with the 7 dead fetuses. No developmental effects were observed in the rat study. The marginal toxicity observed in the rat study was not associated with developmental	The read across approach is supported by RAC.

Date	Country / Person / Organisation / MSCA	Comment	DS response to comment	RAC response to comment
		common degradates which are thioglycolic acid and C-8 alcohols (either 2-ethylhexanol or iso-octanol). 2-EHMA and IOMA have similar physicochemical and toxicological properties. DMT(2-EHMA) and DMT(IOMA) are considered toxicologically equivalent. In the OECD SIDS report, reprotoxic effects were also reported for 2-EHMA (NOAEL: 50 mg/kg/d). As DMTC shows lower NOAEL (10 mg/kg/d) for reproductive/developmental toxicity, using data for DMTC to regulate DMT(2-EHMA) was considered to be health protective for the reproduction/developmental endpoint (Remark: in OECD SIDS 2006, 2-EHMA is referred as EHTG and IOMA, as IOTG). Effects on the development are demonstrated in the 4 key studies and in the supporting study, in the different species (rats, rabbits and mice) in presence of a slight maternal toxicity: 1) Maternal toxicity: - DOT(IOMA) and DOTC show effects on the thymus of maternal animals in rats (Appel and Waalkens, 2004; Anonymous, 1997) and in mice (Faqi, 2001). - A third study with rats (Battenfeld, 1991) reports a slight, but not significant decrease in corrected body weight and corrected body weight gain of the dams (largely attributed to one dam). One question could be raised here: is this dam related to the 7 dead foetuses? - In rabbits (Battenfeld, 1992), a slight maternal toxic effect is mentioned in the dossier but without specifying which kind of effect. 2) Gestational parameters +(maternal toxicity): Amongst others, the following developmental effects are reported: * Significant reduction in fetal body weight: - With rabbits (Battenfeld, 1992)(at 100 mg/kg/d). (only a slight maternal toxic effect) - With mice (Faqi, 2001)(from 67 mg/kg/d). (no signs of toxicity, no reduction in maternal weight gain, no significant reduction of the thymus weight at 67 mg/kg even if significant reduction at 45 mg/kg) * Increased post-implantation loss: - In rats : 49% at 100 ppm and 70% at 300 ppm (Appel and Waalkens, 2004).(Maternal toxicity: decrease thymus weight with histopathological effects.)	effects. This is amended in the dosser. In the rabbits study (Battenfeld, 1992), the authors concluded on a slight maternal toxicity which was substantiated by 4 abortions/21 females (19% in contrast to 4.3% in controls). Amended in the text.	No signs of maternal toxicity were noted in rabbits, and RAC therefore

Date	Country / Person / Organisation / MSCA	Comment	DS response to comment	RAC response to comment
		- In rabbits: at 100 mg/kg/d (Battenfeld, 1992).(only a slight maternal toxic effect) - In mice: resorption rates were significantly increased from 67 mg/kg/d. (no signs of maternal toxicity, no reduction in maternal weight gain, no significant reduction of the thymus weight at 67 mg/kg even if significant reduction at 45 mg/kg.) * Significantly increased incidence of abortion: - In rabbits: at 100 mg/kg/d (Battenfeld, 1992).(only a slight maternal toxic effect) * Increased number of stillbirths: - In rats: in the second generation of the 2-generation study (at 200 ppm) (26 vs. 5 in controls)(significant decrease in relative maternal thymus weight)(Anonymous, 1997) and in the study of Appel and Waalkens, 2004, which shows decreased live birth index (53% at 100 ppm, 60% at 300 ppm) (decrease in thymus weight and increases in kidney and liver weights at all doses (10, 100 ppm, 300ppm), histopathological effects at 100 and 300 ppm, no clinical signs, no effects on food conversion. Decreased body weight associated with reduced food consumption at 300 ppm, attributed to reduced palatability). Moreover, Battenfeld (1991) reported seven dead foetuses in one litter at 25 mg/kg/d (but it is not known if the litter concerned is the litter of the dam showing an important body weight decrease). 3) Variations and malformations in the foetuses +(maternal toxicity): * Minor visceral anomalies: - In rabbits (Battenfeld, 1992): at 100 mg/kg/d, severely dilated renal pelves and additional small vessels originating from the aortic arch. (only a slight maternal toxic effect) * Minor skeletal head anomalies: - In rabbits (Battenfeld, 1992): at 100 mg/kg/d, incompletely ossified bones in the skull. (only a slight maternal toxic effect) * Significant increase in skeletal variations: - In rabbits (Battenfeld, 1992): at 100 mg/kg/d, not or incompletely ossified sternebrae and feet bones. (only a slight maternal toxic effect) - In mice (Faqi, 2001): Unossified digit and supernumerary cervical ribs (at 23 and 45 mg/kg/d), Supernumerary lumbar or cervical ribs (at 23, 30 and 45 mg/kg/d), Hindpaw incompletely		view the abortions as signs of reproductive toxicity rather than of maternal toxicity.

Date	Country / Person / Organisation / MSCA	Comment	DS response to comment	RAC response to comment
		ossified, os frontale misshapened and interparietale incompletely ossified (at 45 mg/kg/d). * Significant increase in skeletal abnormalities: - In mice (Faqi, 2001): from 67 mg/kg/d, which include bent forelimbs, bent hindlimbs, dislocated sternum, bent ribs.(no signs of toxicity, no reduction in maternal weight gain, no significant reduction of the thymus weight at 67 mg/kg even if significant reduction at 45 mg/kg). * Significant incidence of cleft palate: - In mice (Faqi, 2001): from 67 mg/kg/d. (no signs of toxicity, no reduction in maternal weight gain, no significant reduction of the thymus weight at 67 mg/kg even if significant reduction at 45 mg/kg). * Significant incidence of exencephaly: - In mice (Faqi, 2001): at 100 mg/kg/d. (no signs of toxicity, no reduction in maternal weight gain, significant reduction of the thymus weight at 100 mg/kg). 4) Conclusions on the developmental effects and the proposed classification: Serious developmental effects are observed in 5 studies, in 3 species. Variations are seen in mice and rabbits, malformations are seen in mice (notably bent forelimbs (at 67 and 100 mg/kg) , cleft palate (at 67 and 100 mg/kg) and exencephaly (at 100 mg/kg)), while rats show amongst others high post-implantation losses (70% at 300 ppm). For some of these effects, there are clear dose-response relationships (variations-malformations in mice, post-implantation losses in rats). Most developmental effects occur in the presence of slight maternal toxicity, whereas other occur in the absence of maternal thymus toxicity (malformations in mice at 67 mg/kg/d). Although maternal toxicity might have had an influence, the relation between the maternal toxic effect (toxicity of the thymus) and the developmental effects observed is not established. In conclusion, in our opinion, given the severity of the findings in the offspring a classification as Repr. Cat. 1b – H360D is warranted for DOT(2-EHMA). The harmonized classification for DOTC should be revised accordingly. A similar harmonized classification for DOT(IOMA) should be considered as well.		RAC supports the notion that the data better fits the criteria for repro Cat 1B rather than Cat 2.
09/05/2011	Denmark / Trine Thorup Andersen /	Page 4: Denmark does not agree with the proposed classification for Dioctyltin bis(2-ethylhexyl mercaptoacetate) for reproduc-tive toxicity in category 2 with H361d. Specific comments are included in the file attached.	Section 4.11.15 is	Information

Date	Country / Person / Organisation / MSCA	Comment	DS response to comment	RAC response to comment
	Member State	*ECHA's comment: The attachment "Danish Comments on proposed classification of DOT(2-EHMA).doc" is copied below:* Regarding the proposed classification of Dioctyltin bis(2-ethylhexyl mercaptoacetate) for reproductive toxicity (Repr. Cat. 2; H361d) Based on the current CLH report, Denmark does not agree with the proposed classification for Dioctyltin bis(2-ethylhexyl mercaptoacetate) (re-ferred to as DOT (2-EHMA)) for reproductive toxicity in category 2 with H361d. Generally we find that the argumentation for the proposed classifi-cation is not clear and is not justified according to the criteria. In "Section 4.11.15 Comparison with criteria" only some of the relevant findings in the reproductive toxicity studies are summarized, i.e. those from the two generation study and the reprotoxicity screening study. However, the findings in the developmental toxicity studies are not included in this section. A summary is given on page 36 in the CLH report and the results are considered quite relevant for comparison with criteria as the results show developmental toxicity effects in three studies in rats, mice and rabbits at dose levels causing no or slight maternal toxicity. Consequently, we find that these data should be included in "Section 4.11.15 Comparison with criteria". In the same section, the heading implies that there should be a comparison with criteria, but this is not included. Actually this section concludes without any discussion or comparison with criteria that DOT (2-EHMA) is "classified with…. 'Reprotoxicity category 2' H361 according to CLP". We have compared the results with the CLP criteria for category 1B and category 2 (see Table 1). The criteria states that category 2 may be more appropriate that category 1 when there is mechanistic information that raises doubt about the relevance of the effect for humans, the evidence is not sufficiently convincing or deficiencies in the study make the quality of evidence less convincing. We find that none of these arguments are rele-vant in this case where there is a quite extensive database comprising 5 guideline or standard reproductive toxicity studies all showing developmental toxicity effects in three	amended accordingly.	has been added, but the comparison with the criteria is not sufficiently improved.

Date	Country / Person / Organisation / MSCA	Comment	DS response to comment	RAC response to comment
		animal species at dose levels causing no or slight maternal maternal toxicity. Consequently, we find that DOT (2-EHMA) should be classified with Category 1B based on the results in the two-generation study, the reprotox screening study and the three developmental toxicity studies. Table 1 - CLP criteria for reprotoxicity category 1B and 2 CATEGORY 1 Known or presumed human reproductive toxicant Category 1B Presumed human reproductive toxicant The classification of a substance in this Category 1B is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic ef-fects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mecha-nistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate. CATEGORY 2 Suspected human reproductive toxicant 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 devel-opment, 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. Kind regards Trine Thorup Andersen, Danish Environmental Protection Agency, Chemicals		RAC fully supports the notion that the data better fits the criteria for repro Cat 1B rather than cat 2.
09/05/2011	United Kingdom / Member State	Page 30 – section 4.11 – toxicity for reproduction – Please state the numbers of animals used at each dose for all of the reproductive toxicity studies.	Text amended accordingly.	

Date	Country / Person / Organisation / MSCA	Comment	DS response to comment	RAC response to comment
		Page 33 – section 4.11.4 – summary and discussion of reproductive toxicity – If available, this section would benefit from some additional information. Including, the incidence rates for each reported adverse effect, historical control data for these effects and the number of animals effected at each dose; to help in interpretation of the data and allow the reader to identify dose related trends. Page 33 – section 4.11.4 – summary and discussion of reproductive toxicity – For completeness, it would be useful if you could provide more information on the maternal toxicity observed. Such as, a description of the observed effects, an indication of the severity and the dose at which the effect occurred. Page 35- section 4.11.4 – summary and discussion of reproductive toxicity – developmental toxicity – To avoid confusion please correct subtitle 2 to say 'In the mice developmental study (Faqi, 2001)'. Page 37- section 4.11.5 – comparison with the criteria- Please expand this section to include an explanation as to why it was considered that the effects observed in the reproductive toxicity studies best fit the criteria for classification in category 2 (CLP).		Information has been added, but the comparison with the criteria is not sufficiently improved.

Respiratory sensitisation

Date	Country / Person / Organisation / MSCA	Comment No comments received.	DS response to comment	RAC response to comment

Other hazards and endpoints

Date	Country / Person / Organisation / MSCA	Comment	DS response to comment	RAC response to comment
06/05/2011	Sweden / Member	Sensitisation Although not being a harmonised endpoint, we would like to point out that the self-	Done. DOTE is proposed to be	Noted

Date	Country / Person / Organisation / MSCA	Comment	DS response to comment	RAC response to comment
	State	classification needs to address which of the sensitization categories (1A/1B) the substance should be classified in	classified Skin sensitizer category 1 A in the CLH dossier	
09/05/2011	United Kingdom / Member State	Page 13- section 4.1.3 – summary and discussion of toxicokinetics- you state that DOTE readily hydrolysed to DOTC by 101% in 30 minutes. Should this be 100% in 30 minutes? Page 13- Section 4.1.3- summary and discussion of toxicokinetics- the Yoder (2000) toxicokinetic study referred to in this section of the CLH report is missing from Table 10. Please include a summary of this study in Table 10.	101% is the result indicated in the study report. Text corrected, the Author "anonymous" is Yoder	

ATTACHMENTS RECEIVED:

- MSCA Denmark: Danish Comments on proposed classification of DOT(2-EHMA).doc

Annex 2.2: The report below is a revision of the original CLH report that was performed by the dossier submitter as part of the response to comments received under public consultation.

CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2

Substance Name: Dioctyltin bis(2-ethylhexyl mercaptoacetate)

EC Number: 239-622-4

CAS Number: 15571-58-1

Index Number: /

Contact details for dossier submitter: ARKEMA on behalf of ETINSA

Version number: 3 UPDATED 2011 06 29 **Date: June 2011**

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Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	Dioctyltin bis(2-ethylhexyl mercaptoacetate)
EC number:	239-622-4
CAS number:	15571-58-1
Annex VI Index number:	/
Degree of purity:	≥ 80% (w/w)
Impurities:	Mono-n-octyltin tris(2-ethylhexyl mercaptoacetate) (CAS N° 27107-89-7) < 20% (w/w);

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	/	/
Current proposal for consideration by RAC	Repr. Cat. 2 – H361d	Repr. Cat. 3; R63
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)		

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)]
3.7.	Reproductive toxicity	Reprotoxicity Category 2 H361d: Suspected of damaging the unborn child	/	/	

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

Labelling:

Signal word	Warning
Hazard statements	H361d: Suspected of damaging the unborn child
Precautionary statements	P202: Do not handle until all safety precautions have been read and understood. P280: Wear protective gloves/protective clothing/eye protection/face protection P308+P313: IF exposed or concerned: Get medical advice/attention.

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)]
Toxicity to reproduction – development	Reprotoxicity Category 3 R63: Possible risk of harm to the unborn child.	/	/	

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

Labelling:

Indication of danger	
R-phrases	R63: Possible risk of harm to the unborn child.
S-phrases	S36/37/39: wear suitable protective clothing, gloves and eye/face protection

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Not covered.

2.2 Short summary of the scientific justification for the CLH proposal

Toxicity for reproduction :

Under the experimental conditions of a two generation study according to OECD 416 (Anonymous,, 1997) on a mixture of DOT(IOMA) and MOT(IOMA) (78.8:16.9%), used as adequate read-across substance, as DOT(IOMA) is a structural analogue to DOT(2-EHMA), the NOAEL for the F0 parental generation was 20 ppm in diet (~1.5 mg/kg bw/day), based on a reduction in the relative thymus weight of males at 60 ppm in diet (~4.7 mg/kg bw/day). The NOAEL for the F1 generation until weaning was 20 ppm (~1.6 mg/kg bw/day), based on a decrease in relative thymus weight in male and female pups at 60 ppm. The NOAEL for the F1 generation post-lactation was 20 ppm, based on a slight decrease in the relative thymus weight of males and an increase in stillbirth at 60 ppm. Indices of mating, fertility, gestation and the pregnancy rates were within the range of the control group at 20 and 60 ppm. The mean pre-coital time, duration of pregnancy in days and duration in hours did not show any substance related effects at all dose-levels. The fertility index was slightly decreased at 200 ppm but was within the range of historical control data. In addition, the viability and lactation indices were decreased at 200 ppm in both the F0 and F1 generation, this was associated with a slightly decreased in pups body weight (by 3 to 4%) in the F0 generation and a significant decrease in pups weight in the F1 generation (males pups between approx. 3% and 19%; female pups between approx 4% and 21%, at $p<0.01$) during the lacation period.

In addition, there is a GLP screening reprotoxicity study according to OECD guideline 421 (Appel and Waalkens, 2004) performed with the hydrolysis product dioctyltin dichloride (3542-36-7) available, which is also an adequate read-across substance based on experimental toxicokinetic data. In this GLP key study, comparable effects were obtained with the two generation study, indeed maternal toxicity substantiated by thymus effect (decreased thymus weight associated with moderate to severe lymphoid depletion) were also recorded at all dose-levels. Dose-related effects were seen at 10, 100 and 300 ppm in diet, with post-implantation losses in the top two dose groups. The maternal LOAEL was set at 10 ppm diet (equivalent 0.7 mg/kg bw/day for males and 0.5-0.7 mg/kg bw/day for females) for treatment related effects to dams included lymphoid depletion.

Developmental toxicity;

The two generation study and developmental toxicity studies in mice, rats and rabbits with mixed DOT(IOMA):MOT(IOMA) (78.8:16.9, 80:20 ratio) showed maternal effects on the thymus, dose-related retardations and variations in mice and rabbits, increased post-implantation losses, and decreased fetal weight plus decreased fetal viability in mice and rabbits. Compared to the screening study with DOTC, it can be concluded that in the comparable period of pregnancy, the effects on fetal weight and viability were basically the same. In contrast, rats did not show any variations of bone formation seen in mice and rabbits.
Serious skeletal malformations (bent forelimbs, bent hindlimbs, dislocated sternum, fused or bent ribs and bent vertebral column) are seen in mice only at the maternal toxic doses of 67 and 100 mg/kg bw/day.

From the three developmental studies in rat, mice and rabbits performed according to or equivalent to OECD Guideline 414, the following NOAEL could be derived:

The NOAEL for maternal toxicity and embryofetal development in the rat study (Battenfeld, 1991) were set at 5 mg/kg bw/day (based on decrease in maternal body weight gain and increase in the percentage of dead fetuses at 25 mg/kg bw/day). The NOAEL for skeletal malformations and variations was the highest tested dose of 25 mg/kg bw/day.

In the mice study (Faqi, 2001), the embryofetal NOAEL for malformations was reported at 45 mg/kg bw/day based on an increased incidence of clef palate in fetuses from dams given 67 mg/kg bw/day. A NOAEL for skeletal variations could not be determined, but would be expected to be <20 mg/kg bw/day, based on an increased incidence of supernumerary lumbar ribs observed at 20 mg/kg bw/day. The NOAEL for maternal organ toxicity was 30 mg/kg bw/day, based on a significant decrease in thymus weight at 45 mg/kg bw/day.

In the rabbit study (Battenfeld, 1992), the NOAEL for developmental and maternal toxicity was set at 10 mg/kg bw/day The evaluation of reproduction data and fetal development indicated a slight embryofetal and moderate retardative effect at 100

mg/kg bw/day (significantly increased incidence of abortion, increase incidence of post-implantation losses, increased incidence of external and visceral malformation) while maternal toxicity was slight.

.In the two generation study reported above (Anonymous, 1997), immune developemental effects were observed in the F0 and F1 progeny as shown by the decreased in the relative thymus weight from 60 ppm (approx. 4.7 mg/kg bw/day). In addition, the viability index was markedly decreased and the pup weight was significantly decreased at 200 ppm in both F0 and F1 generation

The above reported effects (increased post-implantation loss, increase incidence of resorption, increase pups mortality, depressed fetal weight) are indicative of developmental effects. These effects observed in all the above reported studies were almost always associated with maternal toxicity (**substantiated most of the time by a significant thymotoxicity characterized by a decreased in thymus weight and by a moderate to severe lymphoid depletion at microscopic examination), which may indicated that they could have been secondary effects to maternal toxicity**.
It is well-known that the thymus which is reported to have a crucial role during pregnancy (Clarke et al., 1994) is the target organ of organotins (Gennari publications). Although the mechanism of action of thymus involution on embryo development is still unclear, it could be considered as a secondary specific maternally-mediated mechanism which is, according to CLP criteria, correspond to a classification in category 2 for reproductive toxicity.

In addition, the fact that all these studies were performed with either DOTC, the hydrolysis product, or DOT(IOMA) an isomer of DOT(2-EHMA) make the quality of evidence, particularly with respect to comparative dose levels, less convincing as they were not performed on the substance it self.

Based on these effects, DOT(2-EHMA) is proposed to be classified with R63: 'Possible risk of harm to the unborn child' according to Directive 67/548/EEC and 'Reprotoxicity category 2', H361d according to regulation EC no.1272/2008 (CLP).

2.3 Current harmonised classification and labelling

The substance is not currently classified in Annex VI of Regulation EC N° 1272/2008.

2.4 Current self-classification and labelling

Industry self-classification is proposed for this substance for inclusion on the publicly available classification and labelling database.

2.4.1 Current self-classification and labelling based on the CLP Regulation criteria

Table 5: Self-classification and labelling according to CLP

Classification	
Acute toxicity Category 4 – H302 Skin sensitisation Category 1 A – H317 Reprotoxicity Category 2 – H361d STOT Repeated .Exposure Category 1 – H372 Aquatic acute & chronic 1 – H410	
Labelling	
Signal word	Danger
Hazard statements	H302: Harmful if swallowed H317: May cause an allergic skin reaction H361d: Suspected of damaging the unborn child H372: Causes damage to organs (thymus) through prolonged or repeated exposure (oral) H410: Very toxic to aquatic life with long lasting effects
Precautionary statements	P202: Do not handle until all safety precautions have been read and understood. P260: Do not breathe dust/fume/gas/mist/vapours/spray.

	P273: Avoid release to the environment P280: Wear protective gloves/protective clothing/eye protection/face protection P308+P313: IF exposed or concerned: Get medical advice/attention. P501: Dispose of contents/container to licensed hazardous waste disposal agent/site in accordance with local, national and regional legislation..

2.4.2 Current self-classification and labelling based on DSD criteria

Table 6: Self-classification and labelling according to DSD

Classification	
Xn – R22 Xi – R38 R43 T- R48/25 Reprotoxicity Category 3 – R63 N – R50/53	
Labelling	
Indication of danger	T: Toxic N: Dangerous for the environment
R-phrases	R22: Harmful if swallowed R48/25: Toxic, danger of serious damage to health by prolonged exposure if swallowed R38: Irritating to skin R43: may cause sensitization by skin contact R63: Possible risk of harm to the unborn child. R50/53: Very toxic to aquatic organisms may cause long-term adverse effects in the aquatic environment.
S-phrases	S24: Avoid contact with skin S36/37/39: wear suitable protective clothing, gloves and eye/face protection S60 - this material and its container must be disposed of as hazardous waste S61: avoid release to the environment. refer to special instructions/safety data sheets.

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

According to article 36(1), a substance that fulfils the criteria set out in Annex I of the CLP regulation for the following shall normally be subject to harmonised classification and labelling in accordance with Article 37:

(d) reproductive toxicity, category 1A, 1B or 2 (Annex I, section 3.7).

According to Article 37, a manufacturer, importer or downstream user of a substance may submit to the Agency a proposal for harmonised classification and labelling of that substance and, where appropriate, specific concentration limits or M-factors, provided that there is no entry in Part 3 of Annex VI for such a substance in relation to the hazard class or differentiation covered by that proposal..

Currently DOT(2-EHMA) fulfills criteria of both articles 36(1) & 37. In agreement with these articles, reproductive toxicity is proposed for harmonization in this dossier. Toxicokinetic information and other toxicological data are displayed for information so as to provide a general toxicological profile on DOT(2-EHMA) but are not proposed for harmonization.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

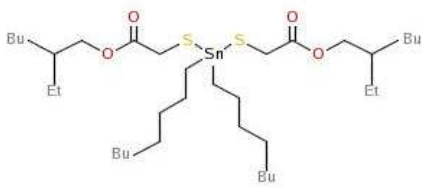
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 5: Substance identity

EC number:	239-622-4
EC name:	2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate
CAS number:	15571-58-1
CAS name	Dioctyltin bis(2-ethylhexyl mercaptoacetate)
IUPAC name:	2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecan-1-oate
CLP Annex VI Index number:	/
Molecular formula:	$C_{36}H_{72}O_4S_2Sn$
Molecular weight range:	751.7945

Structural formula:



Several substances with their acronyms are mentioned in the dossier. For clarity purpose, the names used through the dossier are listed below (see explanation for read-across approach in section 4).

CAS no	EC no	EC name	Synonyms
15571-58-1	239-622-4	2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate	Dioctyltin bis(2-ethylhexyl mercaptoacetate) Dioctyltin bis(2-EHMA) Dioctyltin (2-EHMA)

			DOTE DOT(2-EHMA)
26401-97-8	247-666-0	diisooctyl 2,2'-[(dioctylstannylene)bis(thio)]diacetate	Dioctyltin bis(IOMA) DOT(IOMA) DOT(2-EHMA)
3542-36-7	222-583-2	dichlorodioctylstannane	Di-n-octyltin dichloride Dioctyltin dichloride DOTC
27107-89-7	248-227-6	2-ethylhexyl 10-ethyl-4-[[2-[(2-ethylhexyl)oxy]-2-oxoethyl]thio]-4-octyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate	Mono-octyltin tris(2-ethylhexyl mercaptoacetate) Monooctyltin (2-EHMA) Octyltin tris(2-EHMA) MOTE MOT(2-EHMA)
26401-86-5	247-665-5	triisooctyl 2,2',2''-[(octylstannylidyne)tris(thio)]triacetate	Octyltin tris(IOMA) MOT(IOMA) MOT(IOTG)

1.2 Composition of the substance

Dioctyltin bis(2-ethylhexyl mercaptoacetate) [DOT(2-EHMA)] is always manufactured with mono-octyltin tris(2-ethylhexyl mercaptoacetate) [MOT(2-EHMA), CAS No. 27107-89-7] as the major impurity.. Moreover, it should be considered that the concentration ratio between [DOT(2-EHMA)] and [MOT(2-EHMA)] can differ depending on the manufacturer of the substance.
The CLH report and classification and labelling proposal for DOT(2-EHMA) have been established based on a purity of minimum 80% in reproductive toxicity studies. Regarding the substance identity, dioctyl bis(2-ethylhexyl mercaptoacetate) will be then considered as a mono-constituent substance.

Table 6: Constituents (non-confidential information)

Constituent	**Typical concentration**	**Concentration range**	**Remarks**
Dioctyltin bis(2-ethylhexyl mercaptoacetate) EC no: 239-622-4		≥ 80 % (w/w)	

Current Annex VI entry: not relevant

Table 7: Impurities (non-confidential information)

Impurity	**Typical concentration**	**Concentration range**	**Remarks**
Mono-n-octyltin tris(2-ethylhexyl mercaptoacetate) EC no.: 248-227-6		< 20 % (w/w)	
2-ethylhexyl mercaptoacetate EC no.: 231-626-4		0-0.5% (w/w)	
dichlorodioctylstannane EC no.: 222-583-2		0.-0.5% (w/w)	

Current Annex VI entry:

Dichlorodioctylstannane, index number 050-021-00-4.

Table 8: Additives (non-confidential information)

Additive	**Function**	**Typical concentration**	**Concentration range**	**Remarks**
/	/	/	/	/

Current Annex VI entry: not relevant

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	Liquid, clear colourless to slightly yellow		
Melting/freezing point	-39°C		
Boiling point	No boiling point could be measured by DSC.		The substance decomposes at T >275°C and normal pressure without boiling.
Relative density	1.07 g/cm^3 at 20°C		
Vapour pressure	< 2.50 x 10^{-4} Pa		Due to the behaviour of the test material in the equipment, an exact value for the vapour pressure could not be calculated. Three tests were performed. Significant differences between the individual measurements were observed. The vapour pressure was therefore reported to be lower than the highest measured value at < 2.50 x 10^{-4} Pa
Surface tension	/		not technically feasible as the water solubility of the substance is less than 0.1mg/l.
Water solubility	The following statement was included in a physico-chemical properties study by Baltussen (2010) concerning the feasibility of a water solubility study on the test substance: "The test substance rapidly decomposes in contact with water forming a range of breakdown products. The test substance can only be analysed after derivatisation, but using derivatisation, a distinction between intact test substance and breakdown products can no longer be made. It is not possible to specifically analyse the intact test substance with any technique at low levels which is required due to the expected low water solubility of the test substance" It was concluded that the test on the water solubility of the test substance could not be performed		study technically not feasible
Partition coefficient n-octanol/water	A statement concerning the partition coefficient of the test material was included in the physico-chemical		study technically not feasible

	testing battery by Baltussen (2010): "The test substance rapidly decomposes in contact with water forming a range of breakdown products. The test substance can only be analysed after derivatisation, but using derivatisation, a distinction between intact test substance and breakdown products can no longer be made. It is not possible to specifically analyse the intact test substance with any technique at low levels which is required due to the expected low water solubility of the test substance." The author concluded that the study is not technically feasible.		
Flash point	182°C		Pensky-Martens closed cup method.
Flammability	Not flammable		
Explosive properties	Not explosive		Expert judgement based on physico-chemical properties and the substance's structure
Self-ignition temperature	390 °C at 989.6 -999.2 hPa.		
Oxidising properties	No oxidising properties		Expert judgement based on physico-chemical properties and the substance's structure
Granulometry	Not relevant		

2 MANUFACTURE AND USES

2.1 Manufacture

Commercial stabilizers consisting of dioctyltin bis(2-ethylhexyl mercaptoacetate) and mono-octyltin tris(2-ethylhexyl mercaptoacetate) are produced from the corresponding mixture of dioctyltin/mono-octyltin chlorides, 2-ethylhexyl mercaptoacetate, and a base. The organotin stabilizer is isolated by phase separation and eventually filtered to remove solids or stripped to remove volatile components.

2.2 Identified uses

Dioctyltin bis(2-ethylhexyl mercaptoacetate is mostly used as a stabiliser in plastic.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Not evaluated in this dossier.

4 HUMAN HEALTH HAZARD ASSESSMENT

*Read across approach for repeated exposure assessment:

This CLH notification applies a read across of mammalian toxicology between three chemicals: Dioctyltin (2-EHMA), Dioctyltin (IOMA), and Dioctyltin dichloride. These substances are all members of the dioctyltin family of compounds, and the read across characteristics for this family were discussed in depth under the HPV program: SIDS Initial Assessment Reports "Dioctyltin dichloride and selected thioesters".

The dioctyltins are tetravalent tin compounds comprised of two octyl groups bound to tin through tin-carbon bonds, and two other labile groups bound to tin. These other labile groups can react easily, and are hydrolytically removed in reactions with water, or under other conditions

A simulated gastric hydrolysis study of DOT(2-EHMA) was conducted and demonstrated that DOT(2-EHMA) readily hydrolyzed to dioctyltin dichloride (DOTC) under physiological conditions. Within 0.5 hours, 100% hydrolysis of the test compound occurred (ORTEP Association Stabilizer Task Force 2000). Thus, DOTC is an appropriate anchor compound and surrogate for the mammalian toxicology endpoints of repeated dose, *in vivo* genetic toxicity, reproduction, and developmental effects, when they are assessed using oral administration.

We note that this approach also is justified by several reviews which clearly show that the mammalian toxicology of alkyltins is primarily dependent on the number and type of alkyl groups attached to tin, and not on the other ligands that can undergo hydrolysis from the tin (Hoch 2001; Snoeij et al. 1987; Molloy 1989).

Furthermore, read-across at a "analogue level" as described in the above cited SIDS report is applied to data on diisooctyl 2,2'-[(dioctylstannylene)bis(thio)]diacetate (CAS No. 26401-97-8, also named dioctyltin bis(isooctyl mercaptoacetate, DOT(IOMA) is applied. DOT(IOMA) and DOT(2-EHMA) are isomers differing only slightly in the structure of the C-8 alcohol of the mercaptoester ligand (either isooctanol or 2-ethylhexanol, respectively). Since these alcohol are so close in structure, their respective mercaptoacetate esters are expected to have very similar physicochemical and toxicological properties as noted in (SIDS Initial Assessment Report "Esters of Thioglycolic Acid" prepared for SIAM 23 (2006)). On this basis we justify that DOT(2-EHMA) and DOT(IOMA) are analogues, and apply a full read across of all end points between these two dicotyltin substances which are made using these isomers as the alcohol moiety of the mercaptoesters. It is important to note that this level of read across applies only to very special situations for the organotins, where the labile groups are nearly identical, as it is the case for the above substances.

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

Table 10. Overview of experimental studies on absorption, metabolism, distribution and elimination

Method	Results	Remarks	Reference
in vitro study rat and human epidermis dermal Exposure regime: 24 hour(s) Doses/conc.: 17,007 ug tin/cm2 OECD Draft Guideline for Dermal Delivery and Percutaneous Absorption: In Vitro Method [OECD TG 428]	Main ADME results: absorption: Absorption of tin from DOT(2-EHMA) through rat epidermis significantly overestimates absorption through human epidermis. Evaluation of results: bioaccumulation potential cannot be judged based on study results	2 (reliable with restrictions) key study experimental result **Test material (EC name): 2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate**	Ward, R.J. (2003)

in vitro study no data in vitro A simulated gastric reaction study was performed.	Toxicokinetic parameters: Half-life 1st: Half-life 2nd: Metabolites identified: yes Details on metabolites: DOT(2-EHMA) readily hydrolyzed to DOTC under physiological conditions (pH 1 to 2).	2 (reliable with restrictions) key study experimental result **Test material (EC name): 2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate**	Yoder (2000)

4.1.2 Human information

No data is available.

4.1.3 Summary and discussion on toxicokinetics

The results obtained from a *in vitro* gastric hydrolysis study (Yoder, 2000) support the use of DOTC as an appropriate surrogate for mammalian toxicology studies of the corresponding thioesters DOT(2-EHMA)/(IOMA) via the oral route as it was demonstrated that DOT(2-EHMA) readily hydrolized to DOTC under physiological conditions (101% hydrolysis within 30 minutes). Thus, DOTC is an appropriate anchor compound and surrogate for the mammalian toxicology endpoints of repeated dose, *in vivo* genotoxicity reproduction, and developmental effects, when they are assessed using oral administration. Acute toxicity, sensitization, irritation and *in vitro* genotoxicity are not covered under the category approach and were evaluated individually for each material. DOT(2-EHMA) and the corresponding thioesters have been therefore joined into one family in a HPV program, presented and validated at OECD (see SIDS 2006, SIAM 23).

With respect to inhalation and dermal mammalian toxicity, the esters have much higher molecular weights and considerably lower volatility than the chloride. The high molecular weights of the esters reduce their potential for absorption via the dermal route, and their volatility reduces their potential for absorption via the inhalation route relative to the chloride.

The absorption of DOT(2-EHMA) was measured *in vitro* (Ward 2003) though both occluded and unoccluded human and rat epidermis. The absorption through rat epidermis was much faster than through human epidermis:

HUMAN EPIDERMIS: A dose of 17,007 µg tin/cm² was determined to alter the barrier function of the epidermis. From the occluded and unoccluded applications, the rates of tin absorption over the 0-24 h exposure period were below the limit of quantification (0.001 µg/cm²/h). In terms of percent applied tin, 0.0001% was absorbed from the occluded dose, and 0.0001% was absorbed from the unoccluded dose after 24 hours of exposure.

RAT EPIDERMIS: Absorption of tin through rat epidermis was much faster than through human epidermis. From the occluded application, the maximum rate of tin absorption (0.035 µg/cm²/h) occurred during 16-24 hours of exposure, and the mean rate of tin absorption over the whole 24-h exposure period was 0.021 µg/cm²/h. From the unoccluded application, the maximum rate of tin absorption occurred during 12-24 hours of exposure and was 0.033 µg/cm²/h. The mean rate of tin absorption over the whole 24-h exposure period was 0.025 µg/cm²/h. In terms of percent applied tin, 0.003% was absorbed from the occluded dose, and 0.004% was absorbed from the unoccluded dose after 24 hours of exposure. The overall recovery of tin from the test system after 24-h exposure was low and may be due to adsorption of the test substance to the glass equipment used. The recovery was 45.5% (human) and 25.2% (rat) of the applied occluded doses, and 29.6% (human) and 30.5% (rat) were recovered from the unoccluded test systems. Of the recovered tin, 2.1% (human) and 5.5% (rat) were obtained from the surface of the epidermis and donor chamber. The mean amounts of tin absorbed by 24 hours were 0.010 µg/cm² (unoccluded) and 0.011 µg/cm² (occluded) through human epidermis and 0.641 µg/cm² (unoccluded) and 0.547 µg/cm² (occluded) through rat epidermis.

These results show that the absorption of tin from dioctyltin bis(2-ethylhexylmercaptoacetate) through rat epidermis significantly overestimated absorption from human epidermis. By 24 hours only a small amount of the applied tin (3% in human and 1% in the rat) is associated with the epidermis and is not regarded as systemically available.

4.2 Acute toxicity

4.2.1 Non-human information

4.2.1.1 Acute toxicity: oral

Table 11: Summary table of relevant acute toxicity studies

Method	Results	Remarks	Reference
Rat (Tif:RAIf (SPF)) male/female Oral: unspecified Method: OECD Guideline 401 (Acute Oral Toxicity)	LD50: 2000 mg/kg bw (male/female) LD50: < 2000 mg/kg bw (female) LD50: > 2000 mg/kg bw (male)	2 (reliable with restrictions) Key study Experimental result **Test material:** **Dioctyltin bis(2-EHMA: Octyltin tris(2-EHMA) (purity 90:10% mixture)**	Anonymous (1992a)
Rat (Crj: CD(SD)) male/female Oral: gavage Method: EPA OPP 81-1 (Acute Oral Toxicity)	LD50: 1800 mg/kg bw (male/female) LD50: > 2500 mg/kg bw (male) (LD50 was estimated to be 3800 mg/kg; the 95% confidence limits were +- 4631 mg/kg and exceed the LD50 value because the dose response curve for males was extremely shallow) LD50: 1150 mg/kg bw (female)	1 (reliable without restriction) Supporting study **Test material:** **Di(n-octyl)tin dichloride : tri-(n-octyl)tin chloride : n-octyltin trichloride, (purity 95.7: 2.3 :2.0% mixture)**	Auletta, C.S. and Daly, I.W. (1984)
Mouse ("H" (Czech. standard strain; Velaz Corp.)) male/female Oral: gavage Method not reported	LD50: 2010 mg/kg bw (male/female)	2 (reliable with restrictions) Supporting study Experimental result **Test material:** **Dioctyltin bis(2-EHMA (reported as pure sample)**	Pelikan, Z. and E. Cerny (1970)

4.2.1.2 Acute toxicity: inhalation

No study is available for acute inhalation endpoint.

4.2.1.3 Acute toxicity: dermal

Table 11: Summary table of relevant acute toxicity studies

Method	Results	Remarks	Reference
Rat (Tif:RAIf (SPF)) male/female Coverage: semiocclusive Method: OECD Guideline 402 (Acute Dermal Toxicity)	LD50: > 2000 mg/kg bw (male/female)	1 (reliable without restriction) Key study Experimental result **Test material (mixture) :** **Dioctyltin bis(2-EHMA) [CAS No. 15571-58-1]:Octyltin tris(2-EHMA) [CAS No. 27107-89-7] (mixture 70:30%)**	Anonymous (1992)
Rat (Tif:RAIf (SPF)) male/female Coverage: semiocclusive Method OECD Guideline 402 (Acute Dermal Toxicity)	LD0: > 2000 mg/kg bw (male/female) (no mortality)	1 (reliable without restriction) Key study Experimental result **Test material:** **Dioctyltin bis(2-EHMA) : Octyltin tris(2-EHMA) (purity 90:10% mixture)**	Anonymous (1992b)

4.2.1.4 Acute toxicity: other routes

No data is available.

4.2.2 Human information

No data is available.

4.2.3 Summary and discussion of acute toxicity

A robust acute oral toxicity rat study (OECD guideline 401) was carried out with a mixture of DOT(2-EHMA) and MOT(2 -EHMA) (90:10%). Two doses (1000 and 200 mg/kg bw) were tested (single dose) with a 14-days observation period. Animals in both dose groups exhibited clinical signs of toxicity and effects on mortality were observed. The LD50 was lower than 2000 mg/kg for female rats, the overall LD50 for males and females was 2000 mg/kg bw (lower 95% confidence limit= 1265 mg/kg bw). More studies were available and included as supporting information.

A robust acute dermal toxicity rat study (OECD guideline 402) was carried out with a mixture of DOT(2-EHMA) and Octyltin tris(2-EHMA) (90:10 % w/w). The test dose was 2000 mg/kg bw; the dose volume applied was 2 ml/kg bw. After 24 hours, the exposed skin was cleaned and the area of application was observed for 14 days. Due to the lack of observed mortality, the 14-day acute dermal LD50s of the test substance were reported as: LD50 (both sexes) >2000 mg/kg bw. An other study (OECD 402) was carried out with a mixture of DOT(2-EHMA) and MOT(2-EHMA) (70:30%), the same result is observed : LD50 > 2000 mg/kg bw.

No information on inhalation toxicity was available.
Information on acute toxicity is reported here for information only, so as to provide a general toxicological profile on DOT(2-EHMA).

This point is however not proposed for harmonisation.

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

The acute oral and dermal studies didn't identify target organ toxicity in animals treated with DOT(2-EHMA).

4.4 Irritation

4.4.1 Skin irritation

4.4.1.1 Non-human information

Table 12: Summary table of relevant skin irritation studies

Method	Results	Remarks	Reference
Rabbit (New Zealand White) Coverage: semiocclusive (shaved) Method: OECD Guideline 404 (Acute Dermal Irritation / Corrosion) Observation period : 12 days	Moderately irritating (but not classified) Erythema score: 2.1 of max. 4 (mean (6 rabbits)) (Time point: 24-48-72 hours) (fully reversible within: 11 days) (Mean individual scores : 3-2-2-2-1.67-2) Edema score: 0.33 of max. 4 (mean (6 rabbits)) (Time point: 24-48-72 hours) (fully reversible) (Mean individual scores : 1-0-0.33-0-0.33-0.33)	1 (reliable without restriction) Key study Experimental result **Test material:** **Dioctyltin bis(2-EHMA (purity > 98%)**	Varsho B.J. (1996)
Rabbit (New Zealand White) Coverage: (shaved) Method: OECD Guideline 404 (Acute Dermal Irritation / Corrosion) Observation period : 10 days	Moderately irritating (but not classified) Erythema score: 1.78 of max. 4 (mean (3 rabbits)) (Time point: 24-48-72 hours) (fully reversible within: 10 days) (Mean individual scores : 2 - 2 - 1.33) Edema score: 1.33 of max. 4 (mean (3 rabbits)) (Time point: 24-48-72 hours) (fully reversible within: 7 days) (Mean individual scores : 1.67 - 1 - 1.33)	1 (reliable without restriction) Key study Experimental result **Test material:** **Dioctyltin bis(2-EHMA) : Octyltin tris(2-EHMA) (purity 90:10% mixture)**	Anonymous (1992c)

4.4.1.2 Human information

No data is available.

4.4.1.3 Summary and discussion of skin irritation

One acute Dermal Irritation / Corrosion GLP test performed according to OECD 404 was carried out with DOT(2-EHMA) (purity>98%). The test substance was applied undiluted on a patch on shaved rabbit skin. The test material induced slight to moderate erythema on all rabbits and very slight edema on four animals. Three rabbits had desquamation. There were no other dermal findings. All irritations were reversible and completely subsided at day 11 or earlier.

The Primary Irritation Index was calculated to be 2.2.

Information on skin irritation is reported here for information only, so as to provide a general toxicological profile on DOT(2-EHMA).

This point is however not proposed for harmonization.

4.4.2 Eye irritation

4.4.2.1 Non-human information

Table 13: Summary table of relevant eye irritation studies

Method	Results	Remarks	Reference
Rabbit (New Zealand White) TSCA Health Effects Test Guidelines, 40 CFR 798.4500 Method : OECD Guideline 405 (Acute Eye Irritation / Corrosion)	not irritating Cornea score: Cornea opacity score : 0 of max. 4 (mean (6 rabbits)) (Time point: 24-48-72 hours) (All mean individual score is 0) Cornea area score: 0 of max. 4 (mean (6 rabbits)) (Time point: 24-48-72 hours) (All mean individual score is 0) Iris score: 0 of max. 2 (mean (6 rabbits)) (Time point: 24-48-72 hours) (All mean individual score is 0) Conjunctivae score: (Redness) 0.5 of max. 3 (mean (6 animals)) (Time point: 24-48-72 hours) (fully reversible within: 4 days) (Mean individual scores : 0.67-0.67-0.33-1.33-0-0) (Chemosis) 0.22 of max. 4 (mean (6 rabbits)) (Time point: 24-48-72 hours) (fully reversible within: 4 days) (Mean individual scores : 0-0.33-0-1-0-0) (Discharge) 0 of max. 3 (mean (6 rabbits)) (Time point: 24-48-	1 (reliable without restriction) Key study Experimental result **Test material:** **Dioctyltin bis(2-EHMA (purity>98%)**	Varsho, B.J. (1996)

	72 hours) (All mean individual score is 0)		

4.4.2.2 Human information

No data is available.

4.4.2.3 Summary and discussion of eye irritation

One in vivo rabbit eye irritation GLP study performed according to OECD 405 was carried out with DOT(2-EHMA) (purity>98%). The test substance was instilled undiluted in the right lower conjunctival sac. Minor conjunctival irritation was observed, and no iris or corneal effects. Effects were fully reversible within 96h. The test substance was not considered as an eye irritant.

Information on eye irritation is reported here for information only, so as to provide a general toxicological profile on DOT(2-EHMA).

This point is however not proposed for harmonization.

4.4.3 Respiratory tract irritation

No data is available.

4.5 Corrosivity

No data is available.

4.6 Sensitisation

4.6.1 Skin sensitisation

4.6.1.1 Non-human information

Table 15: Summary table of relevant skin sensitisation studies

Method	Results	Remarks	Reference
Guinea pig (Pirbright White Strain (Tif: DHP)) male/female Guinea pig maximisation test Induction: intradermal and epicutaneous Challenge: epicutaneous, occlusive Method: OECD Guideline 406 (Skin Sensitisation)	Sensitising (according to the Regulation EC no.1272/2008 (CLP)) No. with positive reactions: 1st reading: 0 out of 10 (Control group (induction with vehicle)); 24 h after chall.; dose: 30% 2nd reading: 0 out of 10 (Control group (induction with vehicle)); 48 h after chall.; dose: 30% 1st reading: 9 out of 10 (Control group (induction with test article)); 24 h after chall.; dose: 30%	1 (reliable without restriction) Key study Experimental result **Test material:** **Dioctyltin bis(2-EHMA) :Octyltin tris(2-EHMA) (purity 90:10% mixture)**	Anonymous (1993)

	2nd reading: 9 out of 10 (Control group (induction with test article)); 48 h after chall.; dose: 30% 1st reading: 0 out of 20 (Test group (induction with vehicle)); 24 h after chall.; dose: 30% 2nd reading: 0 out of 20 (Test group (induction with vehicle)); 48 h after chall.; dose: 30% 1st reading: 18 out of 20 (Test group (induction with test article)); 24 h after chall.; dose: 30% 2nd reading: 20 out of 20 (Test group (induction with test article)); 48 h after chall.; dose: 30% rechallenge: 0 out of 10 (Control group (induction with vehicle)); 24 h after chall.; dose: 10% rechallenge: 0 out of 10 (Control group (induction with vehicle)); 48 h after chall.; dose: 10% rechallenge: 0 out of 10 (Control group (induction with test article)); 24 h after chall.; dose: 10% rechallenge: 0 out of 10 (Control group (induction with test article)); 48 h after chall.; dose: 10% rechallenge: 0 out of 20 (Test group (induction with vehicle)); 24 h after chall.; dose: 10% rechallenge: 0 out of 20 (Test group (induction with vehicle)); 48 h after chall.; dose: 10% rechallenge: 17 out of 20 (Test group (induction with test article)); 24 h after chall.; dose: 10% rechallenge: 16 out of 20 (Test group (induction with test article)); 48 h after chall.; dose: 10%		
Guinea pig (Pirbright White Strain (Tif: DHP)) male/female Guinea pig maximisation test Induction: intradermal and epicutaneous Challenge: epicutaneous, occlusive Method : OECD Guideline 406	Sensitising No. with positive reactions: 1st reading: 0 out of 10 (Control group (induction with vehicle)); 24 h after chall.; dose: 50% 2nd reading: 0 out of 10 (Control group (induction with vehicle)); 48 h after chall.; dose: 50%	2 (reliable with restrictions) Supporting study Experimental result **Test material: Dioctyltin bis(2-EHMA) : Octyltin tris(2-EHMA)**	Anonymous (1993)

(Skin Sensitisation)	1st reading: 3 out of 10 (Control group (induction with test article)); 24 h after chall.; dose: 50% 2nd reading: 5 out of 10 (Control group (induction with test article)); 48 h after chall.; dose: 50% 1st reading: 0 out of 20 (Test group (induction with vehicle)); 24 h after chall.; dose: 50% 2nd reading: 0 out of 20 (Test group (induction with vehicle)); 48 h after chall.; dose: 50% 1st reading: 17 out of 20 (Control group (induction with test article)); 24 h after chall.; dose: 50% 2nd reading: 20 out of 20 (Control group (induction with test article)); 48 h after chall.; dose: 50% rechallenge: 0 out of 10 (Control group (induction with vehicle)); 24 h after chall.; dose: 20% rechallenge: 0 out of 10 (Control group (induction with vehicle)); 48 h after chall.; dose: 20% rechallenge: 0 out of 10 (Control group (induction with test article)); 24 h after chall.; dose: 20% rechallenge: 0 out of 10 (Control group (induction with test article)); 48 h after chall.; dose: 20% rechallenge: 0 out of 20 (Test group (induction with vehicle)); 24 h after chall.; dose: 20% rechallenge: 0 out of 20 (Test group (induction with vehicle)); 48 h after chall.; dose: 20% rechallenge: 17 out of 20 (Test group (induction with test article)); 24 h after chall.; dose: 20% rechallenge: 15 out of 20 (Test group (induction with test article)); 48 h after chall.; dose: 20%	**(purity 70:30% mixture)**	

4.6.1.2 Human information

No data is available.

4.6.1.3 Summary and discussion of skin sensitisation

A GLP guinea pig maximization test (OECD Guideline 406) was carried out with a mixture of DOT(2-EHMA) and Octyltin tris(2-EHMA) (70:30% w/w). For induction treatment test substance was formulated in peanut oil (5%) or an adjuvant/saline mixture (intradermal); or in vaseline (5%), epidermal.

85 and 80% of animals in the test group exhibited erythema at 24 and 48 hours respectively; 1/5 females exhibited very slight edema at 48 h. Induction treatment was intradermal and epicutaneous. Challenge treatment was epicutaneous (occlusive).
The test substance showed an extremegrade of skin sensitizing potential in albino guinea pigs.The test substance showed an extreme grade of skin sensitizing potential in albino guinea pigs.
A second GLP guinea pig maximization test (OECD Guideline 406) was carried out with a mixture of DOT(2-EHMA) and Octyltin tris(2-EHMA) (90:10% w/w). The test substance was induced intradermal and epicutaneous (two stages). The test substance showed an extreme grade of skin sensitizing potential in albino guinea pigs.

Information on skin sensitization is reported here for information only, so as to provide a general toxicological profile on DOT(2-EHMA).

This point is however not proposed for harmonization.

4.6.2 Respiratory sensitisation

No data is available.

4.7 Repeated dose toxicity

4.7.1 Non-human information

4.7.1.1 Repeated dose toxicity: oral

Table 17: Summary table of relevant repeated dose toxicity studies

Method	Results	Remarks	Reference
Rat (Wistar) male/female Subchronic (oral: feed) 10, 100, 300 ppm (0.7, 6.5-6.8, and 19.3-19.8 mg DOTC/kg bw/day) (nominal in diet) Exposure: 13 weeks (daily) Method: OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents)	LOAEL: 0.7 mg/kg bw/day (nominal) (male/female) based on: test mat. (based on effect on thymic weight. This level was equivalent to 10 mg DOTC/kg in diet (in males and females).) BMDL05: 0.45 mg/kg bw/day (nominal) (female) based on: test mat. (The BMDL of mg/kg bw/day is recommended as a surrogate for a NOAEL for the effect of dioctyltin dichloride on absolute and relative thymus weight) BMD: 0.5 mg/kg bw/day (nominal) (female) based on: test mat. (for decreased absolute and relative thymus weights.)	1 (reliable without restriction) Key study Read-across from supporting substance (structural analogue or surrogate) **Test material:** **Read-across with Dichlorodioctylstannane (CAS no 3542-36-7) (purity 94.1%)**	Appel MJ and Waalkens-Berendsen DH. (2004) Kim J (2004)
Rat (Sprague-Dawley) male/female	NOAEL: 25 ppm (male/female) based on: test mat. (At 50 and	2 (reliable with restrictions)	Anonymous (1974)

Subchronic (oral: feed) 25, 50, and 100 ppm (0, 1.6, 3.3, and 6.6 mg/kg bw/day) (nominal in diet) Exposure: 90 days (continuously) Method equivalent or similar to OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents)	100 ppm : significant dose-related reduction in absolute and relative thymus gland weights. 25 ppm is equivalent to 1.25 mg/kg bw/day, based on a food factor of 0.05.)	Supporting study Experimental result **Test material: Dioctyltin bis(2-EHMA) : Octyltin tris(2-EHMA) (purity 70:30% mixture)**	
rat (Wistar) male/female subchronic (oral: feed) 100, 500, and 1000 ppm (experiment 1) (nominal in diet) 50 and 250 ppm (experiment 2) (nominal in diet) 10 and 25 ppm (experiment 3) (nominal in diet) Exposure: 90 days (continuously) equivalent or similar to OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents)	NOAEL: 10 ppm (male/female) based on: test mat. (reduced thymus weight (10 ppm is equivalent to 0.5 mg/kg bw/day))	2 (reliable with restrictions) Supporting study Experimental result **Test material: Dioctyltin bis(2-EHMA) : Octyltin tris(2-EHMA) : Trioctyltin (2-EHMA) (purity 97: 0.3 : 2.17% mixture)**	Anonymous (1970)

4.7.1.2 Repeated dose toxicity: inhalation

No data is available.

4.7.1.3 Repeated dose toxicity: dermal

No data is available.

4.7.1.4 Repeated dose toxicity: other routes

No data is available.

4.7.1.5 Human information

No data is available.

4.7.1.6 Other relevant information

No data is available.

4.7.1.7 Summary and discussion of repeated dose toxicity

The key study (Apple and Waalkens, 2004) was carried out with the hydrolysis product DOTC (94.1% of purity with monooctyltintrichloride, tetraoctyltin Trioctyltintinchloride, and some butyltinspecies being the main impurities), according to GLP and OECD 408. The data of the latter study was used for “read across” to evaluate repeated exposure with Dioctyltin bis (EHMA) (CAS N0 15571-58-1). Indeed, DOT(2-EHMA) was demonstrated that it readily hydrolysed to Dichlorodioctyltstanane (CAS no.3542-36-7) under physiological conditions (see IUCLID section 7.1.1). Thus

DOTC(Dichlorodioctylstannane) was considered to be an appropriate anchor compound and surrogate for the mammalian toxicology endpoints of repeated dose, in vivo genetic toxicity, reproduction and developmental effects, when they are assessed using oral administration.
In the above study, tested dose levels were 10, 100, 300 ppm DOTC in diet (0.7, 6.5-6.8, and 19.3-19.8 mg DOTC/kg bw/day). No treatment-related changes were observed in clinical signs, food conversion, neurobehavioural testing, ophtalmoscopy and urinary volume and density. The decreased body weight associated with reduced food consumption in males and females of the 300 ppm group was most probably due to reduced palatability of the test item. A number of treatment related changes were observed (decreased in haemoglobin, packed cell volume, mean corpuscular haemoglobin, total white blood cells, absolute numbers of lymphocytes and an increase in prothrombin time). These changes involved the 300 ppm group and were considered toxicologically relevant. Furthermore, a number of treatment-related clinical chemistry changes were observed (decreases in total protein and calcium and increases in alkaline phosphatase, albumin to globulin ratio, bilirubin and bile acids). These changes involved the 100 and 300 ppm groups and were considered toxicologically relevant.

A number of treatment related changes in organ weights were observed (a decrease in thymus weights and increases in kidney and liver weights). These changes involved all dose groups.

The decreased absolute and relative thymus weights observed at all dose-levels was correlated with histopathological effects observed in the 100 and 300 ppm dose groups and were considered adverse effects. The decreased absolute and relative thymus weights in females of the 10 ppm group, although not accompanied by histopathological changes, they were also considered toxicologically relevant. It was considered to reflect a toxicologically-relevant change in the thymus, which was in accordance with the shown toxicity profile of the test substance (i.e. thymotoxicity). A NOAEL for subchronic toxicity was not established for this study. The LOAEL was determined to be 10 ppm DOTC in diet or 0.7 mg DOTC/kg bw/day.

The two old subchronic studies (Anonymous, 1974 and 1970) with mixtures of DOT(2-EHMA)(CAS No. 15571-58-1) and MOT(2-EHMA) (CAS No. 27107-89-7) at 70/30% Dioctyltin (2 -EHMA) /Monooctyltin (2-EHMA) and 97:2.17 % Dioctyltin (2-EHMA) and Monooctyltin (2-EHMA) demonstrated that the substance causes clear target effects substantiated by thymus lymphocyte depletion.

1/<u>In the first subchronic diet non GLP study (Anonymous, 1970),</u> rats were given 100, 500 and 1000 ppm (test 1), 50, 250 ppm (test 2), 10, 25 ppm (test 3) of a mixture of 97:2.17: 0.3 % Dioctyltin (2-EHMA) and Monooctyltin (2-EHMA) and trioctyltin EHMA during 90 days. the following effects were observed:

- Mortality: 9/15 males and 4/15 females died in the 500 ppm diet group; 15/15 males and 14/15 females died in the 1000 ppm diet group;
- Food consumption and food efficiency: slightly, but not significantly reduced at 500 and 1000 ppm.

Haematology:

- Significant decrease of RBC at 100 ppm diet for males, and at 500 ppm diet for females (week 6).
- Significant decrease in percentage of lymphocytes and neutrophils at 500 ppm diet (both sexes) (weeks 6 and 12).
- Significant decrease in hemoglobin content at 100 ppm diet for males (week 12), and at 500 ppm diet for females (weeks 6 and 12).
- Significant decrease in percentage of packed cell volume at 100 ppm diet for males and females (week 12), and at 500 ppm diet for females (week 12).

- Urinalysis: Specific gravity of the urine was significantly decreased and UGOT levels were significantly increased at 500 ppm diet (both sexes). Specific gravity of the urine of females at 100 ppm diet was also significantly decreased.
- Biochemical: The sugar content of the blood was significantly decreased in males and females at 500 ppm diet. SGOT levels were significantly increased in females at 10 ppm diet. SGPT levels were significantly increased in females at 10 ppm diet and in males at 500 ppm diet. SAP levels were significantly increased at 100 and 500 ppm diet for both sexes.
- The water content of the brain was significantly decreased at 500 ppm diet.
- Organ weights: The following statistically significant changes were observed:

  - Terminal body weight: decreased in females at 100 ppm diet, and in males and females at 500 ppm diet;
  - Relative heart weight: increased in females at 500 ppm diet;
  - Relative kidney weight: increased in males and females at 500 ppm diet;
  - Relative liver weight: increased in males at 10 ppm diet and in females at 500 ppm diet;
  - Relative spleen weight: increased in females at 500 pm diet;
  - Relative brain weight: increased in males and females at 500 ppm diet;
  - Relative gonads weight: increased in males at 500 ppm diet;
  - Relative thymus weight: decreased in males and females at 100 and 500 ppm diet

- Histopathology: 2/5 females at 100 ppm diet, and 5/5 males and 5/5 females at 500 ppm diet had almost complete depletion of lymphocytes resulting in a very small thymus with a uniform picture of the remaining reticula parenchyma, which hardly permitted a distinction between cortex and medulla. This damage of the thymus was occasionally accompanied with little active lymph nodes and a slight reduction of splenic lymphoid cells. In the kidney, 3/5 males and 2/5 females exhibited swollen tubular epithelial cells containing a granular or finely vacuolated cytoplasm.

The NOAEL was determined to be 10 ppm diet (equivalent to 0.5 mg/kg bw/day), on the basis of reduced thymus weight at 25 ppm diet. The LOAEL was determined to be 25 ppm diet (calculated as 1.07-1.24 mg/kg bw/day in males and 1.46-1.51 mg/kg bw/day in females). Calculation of dosage was performed using body weights of 340 g (males) and 200 g (females), and average food consumption of 14.6-16.8 g/rat/day (males) and 11.7-12.1 g/rat/day (females).

2/ <u>In the second subchronic non GLP study (Anonymous, 1974),</u> rats were given mixture of 70/30% Dioctyltin (2-EHMA) /Monooctyltin (2-EHMA) at 25, 50 and 100 ppm in diet (equivalent to an average daily intake of 0, 1.6, 3.3 and 6.6 mg/kg bw/day during 90 days. The following relevant effects were observed:

Significant dose-related reduction in absolute and relative thymus weights in the 50 ppm (3.3 mg/kg bw/day) and 100 ppm (6.6 mg/kg bw/day) dose groups.
The NOAEL was determined to be 25 ppm in the diet (calculated as 1.25 mg/kg bw/day, based on a food factor of 0.05)

The reports on these two tests do not contain information on the test substance homogeneity and stability. However, the observed effects are comparable to the results of a reliable 90 days repeated dose toxicity study performed with Dioctyltindichloride, the gastric hydrolysis product of DOT(2-EHMA) (Appel and Waalkens, 2004): In the latter 90 day repeated dose study, the decreased absolute and relative thymus weights observed at all dose-levels (10, 100 and 300 ppm in diet) and was correlated with histopathological effects observed in the 100 and 300 ppm dose groups considered as adverse effects. The decreased absolute and relative thymus weights in females of the 10 ppm group, although not accompanied by histopathological changes was also considered toxicologically relevant. It was considered to reflect a toxicologically-relevant change in the thymus, which was in accordance with the shown toxicity profile of the test substance (i. e. thymotoxicity).
The data of the latter study was used for “read across” to evaluate the dose toxicity of repeated exposure with DOT(2-EHMA). This study is used for read across for DOT(2-EHMA) as it was demonstrated that it readily hydrolysed to Dichlorodioctyltilstanane (CAS no.3542-36-7) under physiological conditions (see section 7.1.1). Thus DOTC (Dichlorodioctylstannane) was considered to be an appropriate anchor compound and surrogate for the mammalian toxicology endpoints of repeated dose, in vivo genetic toxicity, reproduction and developmental effects, when they are assessed using oral administration.
A NOAEL for subchronic toxicity was not established for this study. The LOAEL was determined to be 10 ppm in diet or 0.7 mg DOTC/kg bw/day, based on effects on the thymus.

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

The evaluation of the repeated dose toxicity was based on three studies:

- Two subchronic oral toxicity tests (rat) with mixtures containing a high concentration of DOT(2-EHMA) (70 and 97% purity)- no guideline studies;

- One subchronic toxicity test performed according to OECD 408 guideline with the hydrolysis product dioctyltin dichloride (94.1 % purity) (Appel and Waalkens, 2004).

The use of DOTC study as an appropriate read-across for mammalian toxicology studies of DOT(2-EHMA)/(IOMA) via the oral route is supported based on a simulated gastric reaction study which has shown readily gastric hydrolysis of DOT(2-EHMA) readily hydrolized to DOTC under physiological conditions, Thus, data on DOTC are relevant and adequate for hazard assessment regarding endpoints of repeated dose, in vivo genetic toxicity, reproduction, and developmental effects, when they are assessed using oral administration.

Read across is therefore applied using a valid repeated dose toxicity study performed with DOTC (94%).

No data on dermal or inhalatory repeated dose toxicity are available.

Information on repeated toxicity exposure is reported here for information only, so as to provide a general toxicological profile on DOT(2-EHMA).

This point is however not proposed for harmonization.

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

The evaluation of the repeated dose toxicity was based on three studies:

- Two subchronic oral toxicity tests (rat) with mixtures containing a high concentration of DOT(2-EHMA) (70 and 97% purity)- no guideline studies;

- One subchronic toxicity test performed according to OECD 408 guideline with the hydrolysis product dioctyltin dichloride (92 % purity) (Appel and Waalkens, 2004).

The use of DOTC study as an appropriate read-across for mammalian toxicology studies of DOT(2-EHMA) via the oral route is supported based on a simulated gastric reaction study which has shown readily gastric hydrolysis of DOT(2-EHMA) readily hydrolized to DOTC under physiological conditions, Thus, data on DOTC are relevant and adequate for hazard assessment regarding endpoints of repeated dose, in vivo genetic toxicity, reproduction, and developmental effects, when they are assessed using oral administration.

Read across is therefore applied using a valid repeated dose toxicity study performed with DOTC (94.1%).

No data on dermal or inhalatory repeated dose toxicity are available.

Information on repeated toxicity exposure is reported here for information only, so as to provide a general toxicological profile on DOT(2-EHMA).

This point is however not proposed for harmonization.

4.9 Germ cell mutagenicity (Mutagenicity)

4.9.1 Non-human information

4.9.1.1 *In vitro* data

Table 18: Summary table of relevant in vitro and in vivo mutagenicity studies

Method	Results	Remarks	Reference
Bacterial reverse mutation assay (e.g. Ames test) (gene mutation) Salmonella typhimurium strains TA98, TA1535, TA1537, and TA1538; Saccharomyces cerevisiae D4 (met. act.: with and without) Doses: 0.005, 0.01, 0.1, 1.0, 5.0, and 10.0 ul/plate (20.0 ul/plate was used for strain TA1537 without activation) equivalent or similar to OECD Guideline 471 (Bacterial Reverse Mutation Assay)	Evaluation of results: negative Test results: negative for Salmonella typhimurium strains TA98, TA1535, TA1537, and TA1538; Saccharomyces cerevisiae D4(all strains/cell types tested); met. act.: with and without; cytotoxicity: yes (The test substance was found to be toxic to the strain TA1537 at 10 and 20 ul/plate and to the strains TA1538 and D4 at 10 ul/plate.)	2 (reliable with restrictions) supporting study Experimental result **Test material:** **Dioctyltin bis(2-EHMA) : Octyltin tris(2-EHMA) (purity 70:30% mixture)**	Anonymous (1978a)

Bacterial reverse mutation assay (e.g. Ames test) (gene mutation) Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538 (met. act.: with and without) Doses: 300, 900, 2700, 8100, and 24,300 µg/0.1 ml equivalent or similar to OECD Guideline 471 (Bacterial Reverse Mutation Assay)	Evaluation of results: positive negative for S. typhimurium, other: TA98, TA1535 and TA1538(strain/cell type: TA98, TA1535 and TA1538); met. act.: with and without; cytotoxicity: yes positive (at 300 and 2700 ug/1 ml) for S. typhimurium TA 1537(strain/cell type: TA 1537); met. act.: with; cytotoxicity: yes negative for S. typhimurium TA 1537(strain/cell type: TA 1537); met. act.: without; cytotoxicity: yes negative for S. typhimurium TA 100(strain/cell type: TA 100); met. act.: with; cytotoxicity: yes positive (at 2700 ug/1 ml) for S. typhimurium TA 100(strain/cell type: TA 100); met. act.: without; cytotoxicity: yes	2 (reliable with restrictions) supporting study experimental result **Test material:** **Dioctyltin bis(2-EHMA) : Octyltin tris(2-EHMA) (purity 70:30% mixture)**	Anonymous. (1983)
Bacterial reverse mutation assay (e.g. Ames test) (gene mutation) S. typhimurium TA 1535, TA 1537, TA 98 and TA 100 (met. act.: with and without) Doses: 15, 45, 135, 405, and 1215 µg/0.1 ml equivalent or similar to OECD Guideline 471 (Bacterial Reverse Mutation Assay)	Evaluation of results: negative Test results: negative for S. typhimurium TA 1535, TA 1537, TA 98 and TA 100(all strains/cell types tested); met. act.: with and without	2 (reliable with restrictions) key study experimental result **Test material:** **Dioctyltin bis(2-EHMA) : Octyltin tris(2-EHMA) (purity 70:30% mixture)**	Anonymous (1979)
Bacterial reverse mutation assay (e.g. Ames test) (gene mutation) S. typhimurium TA 100 (met. act.: without) Doses: 0.005, 0.01, 0.1, 1.0, 5.0, and 10 ul/plate The test was performed in accordance with the method of Ames et al. (1975)	Test results: positive for S. typhimurium TA 100(all strains/cell types tested (Salmonella typhimurium strain TA100)); met. act.: without	2 (reliable with restrictions) supporting study experimental result **Test material:** **Dioctyltin bis(2-EHMA) : Octyltin tris(2-EHMA) (purity 70:30% mixture)**	Anonymous. (1978b)

4.9.1.2 *In vivo* data

Method	Results	Remarks	Reference
Micronucleus assay (chromosome aberration) Rat (Wistar outbred Crl) male Oral: gavage 500, 1000, 2000 mg/kg bw (actual ingested (Just before dosing, the animals were weighed and the test substance was dissolved and diluted in corn oil at concentrations of 25, 50 and 100 mg/ml. The orally (by gavage) given dosing volume was 20 ml/kg bw.)) Method: OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test)	Evaluation of results: negative Test results: Genotoxicity: negative (Dichlorodioctylstannane reached the bone marrow in this micronucleus test. The results did not indicate any chromosomal damage and or damage to the mitotic apparatus of the target cells in the bone marrow.) (male/female); toxicity: no effects	1 (reliable without restriction) Key study Read-across from supporting substance (structural analogue or surrogate) **Test material:** **Read-across with Dichlorodioctylstannane (CAS no 3542-36-7) (purity > 99.1%)**	Krul, C.A.M. (2003)
Micronucleus assay (chromosome aberration) Mouse (CFLP) male/female Oral: gavage 2250, 4500, and 9000 mg/kg bw (actual ingested) Method equivalent or similar to OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test)	Evaluation of results: negative Test results: Genotoxicity: negative (male/female); toxicity: yes (bone marrow depression)	2 (reliable with restrictions) Supporting study Experimental result **Test material:** **Dioctyltin bis(IOMA) [CAS no. 26401-97-8]:Octyltin tris(IOMA) [CAS no.26401-86-5] (purity 80:20% mixture)**	Hossack D.J.N, Richold, M. and Richardson, J.C. (1980)

4.9.2 Human information

No data is available.

4.9.3 Other relevant information

No data is available.

4.9.4 Summary and discussion of mutagenicity

<u>In vitro studies: Ames tests</u>

In the key study (1979), an Ames test was carried out with a mixture of 70% dioctyltin bis(2-ethylhexylmercaptoacetate) and 30% mono-octyltin tris(2-ethylhexylmercaptoacetate). This mixture was tested in strains of *Salmonella typhimurium* (TA 1535, TA 1537, TA 98 and TA 100), with or without S9, and there are positive and negative controls. No mutagenic activity was observed in this test.

Others studies were used as supporting studies because they are less complete than the key study. All these studies used the same mixture as the key study, DOT(2-EHMA): MOT(2-EHMA), 70:30%. One of these studies gave negative results, and two old studies showed a (weak) positive response without metabolic activation.

In vitro studies: Mouse lymphoma assay

A GLP study guideline (OECD 473) was available. DOT(2-EHMA) was examined for its potential to induce gene mutations at the TK-locus of cultured mouse lymphoma L5178Y cells, in both the absence and the presence of a metabolic activation system (S9-mix). DOT(2-EHMA) was cytotoxic in both the absence and presence of S9-mix.

In the absence of S9-mix no increase in mutant frequency was observed at any test substance concentration evaluated. In the presence of S9-mix at 72 µg/ml the mutant frequency was significantly increased by 238 mutants per 1,000,000 clonable cells compared to the negative control. Since relatively small intervals (0.85) were used and the increase was observed at a single concentration causing more than 90% cytotoxicity compared to six concentrations causing 50-70% cytotoxicity which showed no increase in mutant frequency, it is concluded that this increase is not indicative for mutagenicity.

It is concluded that under the conditions used in this study, the test substance DOT(2-EHMA) is not mutagenic at the TK-locus of mouse lymphoma L5178Y cells.

In vivo studies
Three micronucleus tests were available. The key study (Krul 2003) was a guideline study (OECD 474), and the test substance was DOTC (CAS no. 3542-36-7), the hydrolysis product (read-across approach). No chromosomal damage and/or damage to the mitotic apparatus of the target cells in the bone marrow was observed. The dose of 2000 mg/kg bw was cytotoxic (reduced number of PE per number of erythrocytes), which is an evidence that DOTC reached the bone marrow.

This supports the conclusion that DOTC does not induce chromosomal damage or damage to the apparatus of bone marrow cells in mammals.

This result is confirmed in the supporting study (Hossack 1980): a mixture of DOT(IOMA): MOT(IOMA), 80:20% failed to show any evidence of mutagenic potential when administered orally. Dioctyltin bis (IOMA) and dioctyltin bis (2-EHMA) are isomers of the same compound and are expected to be chemically and toxicologically equivalent (read-across approach). However, evidence of bone marrow depression was observed, whichis an evidence that test substance reached the bone marrow.

Others *in vivo* studies: DOTC, at dose-levels up to 5000 µg/kg bw, did not increase the number of sister chromatid exchanges in somatic cells of male and female chinese hamsters (1983). A dose of 1.2 mg/l of DOTC gave no indication of genotoxicity in vivo in a covalent DNA binding assay (1988).

Information on mutagenicity is reported here for information only, so as to provide a general toxicological profile on DOT(2-EHMA).

This point is however not proposed for harmonization.

4.10 Carcinogenicity

No data is available.

4.11 Toxicity for reproduction

4.11.1 Effects on fertility

4.11.1.1 Non-human information

Table 20: Summary table of relevant reproductive toxicity studies

Method	Results	Remarks	Reference
Rat (Sprague-Dawley) male/female two-generation study oral: feed	NOAEL (P): 20 ppm (male/female) (based on a reduction in the relative thymus weight of males)	1 (reliable without restriction) Key study read-across from	Anonymous (1997)

20, 60, and 200 ppm (nominal in diet) (25 male/25 female rats per group) Exposure: Duration of dosing of F0 generation males - 10 weeks prior to mating, during mating (3 weeks), and post mating until sacrifice; females - 10 weeks prior to mating and during mating. Mated females continued to receive test diets during gestation and lactation; unmated females received test diets until sacrifice. Test diets were prepared weekly and analyzed for homogeneity and stability. Duration of dosing of F1 generation: males - 14 weeks (starting at the end of lactation prior to mating), during mating (3 weeks), and post mating until sacrifice; females - 14 weeks (starting at the end of lactation prior to mating) and during mating (3 weeks). (continuously (in diet)) Method: OECD Guideline 416 (Two-Generation Reproduction Toxicity Study)	NOAEL (F1): 20 ppm (male/female) (The NOAEL for the F1 generation until weaning was 20 ppm (~1.6 mg/kg bw/d), based on a decrease in relative thymus weights in male and female pups at 60 ppm. The NOAEL for the F1 generation post lactation was 20 ppm, based on a slight decrease in the relative thymus weight of males and an increase in stillbirths at 60 ppm.) NOAEL (teratogenicity): 200 ppm (No teratogenic effect was observed up to and including the highest dose tested)	supporting substance (structural analogue or surrogate) **Test material:** **Dioctyltin bis(IOMA) [CAS no. 26401-97-8]:Octyltin tris(IOMA) [CAS no. 26401-86-5] (purity 78.8 : 16.9% mixture)**	

4.11.1.2 Human information

No data is available.

4.11.2 Developmental toxicity

4.11.2.1 Non-human information

Table 20: Summary table of relevant reproductive toxicity studies

Method	Results	Remarks	Reference
Rat (Han-Wistar SPF) Oral: gavage 1, 5, and 25 mg/kg bw/day (actual ingested) (25 females/group) Exposure: days 6-15 of gestation (once/day x 10 days) Method equivalent or similar to OECD Guideline 414 (Prenatal	NOAEL (maternal toxicity): 5 mg/kg bw/day (slight but nonsignificant decrease in corrected body weight and corrected body weight gain of the dams indicating a marginal maternal toxic effect of the test substance) NOAEL (developmental toxicity): 5 mg/kg bw/day	1 (reliable without restriction) Key study Read-across from supporting substance (structural analogue or surrogate) **Test material:**	Battenfeld, R. (1991)

Developmental Toxicity Study)	(significant increase in the percentage of dead fetuses)	**Dioctyltin bis(IOMA) [CAS no. 26401-97-8]:Octyltin tris(IOMA) [CAS no. 26401-86-5] (purity 80:20% mixture)**	
Rabbit (New Zealand White) Oral: gavage 1.0, 10, and 100 mg/kg bw/day (actual ingested) (23-24 females/group) Exposure: From day 6 through day 18 of gestation, the groups of dams were intragastrically treated once per day with the test substance administered in peanut oil. (once/day x 13 days) Method equivalent or similar to OECD Guideline 414 (Prenatal Developmental Toxicity Study)	NOAEL (developmental toxicity): 10 mg/kg bw/day: Slight non-significant increase in minor skeletal head anomalies (incompletely ossified bones in the skull). 100 mg/kg bw/day: Significantly increased incidence of abortions, post implantation loss, minor visceral anomalies (severely dilated renal pelves and additional small vessels originating from the aortic arch), minor skeletal head anomalies (incompletely ossified bones in the skull), and skeletal variations of the sternum and feet bones (not or incompletely ossified sternebrae and feet bones); and a significant reduction in fetal body weight.)	1 (reliable without restriction) Key study Read-across from supporting substance (structural analogue or surrogate) **Test material:** **Dioctyltin bis(IOMA) [CAS no. 26401-97-8]:Octyltin tris(IOMA) [CAS no. 26401-86-5] (purity 80:20% mixture)**	Battenfeld, R. (1992)
Mouse (NMRI) oral: gavage 20, 30, or 45 mg/kg bw/day (group 1); 67 or 100 mg/kg bw/day (group 2) (actual ingested) (22 to 25 females/group) Exposure: days 6-17 of gestation (once/day x 12 days) Method equivalent or similar to OECD Guideline 414 (Prenatal Developmental Toxicity Study)	NOAEL (maternal toxicity): 30 mg/kg bw/day (Based on a significant decrease in thymus weight at 45 mg/kg bw/day.) NOAEL (developmental toxicity): 45 mg/kg bw/day (based on an increased incidence of cleft palate in fetuses from dams exposed to 67 mg/kg bw/day.)	2 (reliable with restrictions) Supporting study Read-across from supporting substance (structural analogue or surrogate) **Test material:** **Dioctyltin bis(IOMA) [CAS no. 26401-97-8]:Octyltin tris(IOMA) [CAS no. 26401-86-5] (purity 80:20% mixture)**	Faqi, A.S., H. Schweinfurth, and I. Chahoud (2001)

4.11.2.2 Human information

No data is available.

4.11.3 Other relevant information

Table 20: Summary table of relevant reproductive toxicity studies

Method	Results	Remarks	Reference
Rat (Wistar) male, female Oral: feed 10, 100, 300 ppm (nominal in diet) 10 males and 10 females/group Exposure: Duration of exposure: females: daily for 2 consecutive weeks during the premating period, daily during gestation (up to 26 days after study initiation) and up to euthanasia at or shortly after postnatal day (PN) 4. (daily); males: daily for 13 weeks prior to mating Method: OECD Guideline 421-reproduction/ developmental screening study (sub-chronic (13 week) oral toxicity study in rats (OECD Test guideline 408), including a satellite group for a reproduction/developmental screening study (OECD Test guideline 421)	NOAEL (reproduction toxicity): 10 ppm (0.5 — 0.7 mg/kg bw/day (female)) (Based on reproductive and developmental effects: animals showing only implantations at necropsy, animals delivering only dead pups, decreases in gestation, live birth and viability indices and increases in post-implantation loss and number of runts) LOAEC (general toxicity): 10 ppm (0.5 — 0.7 mg/kg bw/day (female)) (decreases in absolute and relative thymus weights associated with treatment related lymphoid depletion at 10, 100 and 300 ppm groups)	1 (reliable without restriction) Key study Read-across from supporting substance (structural analogue or surrogate) **Test material:** **Read-across with Dichlorodioctylstannane (CAS no 3542-36-7) (purity 94%)**	Appel, M.J. and D.H. Waalkens-Berendsen. (2004)

4.11.4 Summary and discussion of reproductive toxicity

Effects on fertility

In the two generation study performed under GLP and according to OECD 416 (Anonymous, 1997), a mixture of 78.8 % Dioctyltin bis(IOMA) (CAS No. 26401-97-8) and 16.9% Octyltin tris(IOMA) (CAS No. 26401-86-5) was administered to the F0 generation 10 weeks prior to mating, during mating (3weeks) and post-mating. Dioctyltin bis (IOMA) and dioctyltin bis (2-EHMA) are isomers of the same compound and are expected to be chemically and toxicologically equivalent. The F1 generation was treated 14 weeks during premating, 3 weeks during mating. Females continued to receive the test material during gestation and lactation.

The following treatment-related effects were observed:

F0 generation:

- Mortality: 1 male died at 200 ppm diet
- No substance-related mortality or changes in behaviour or external appearance
- Absolute food consumption reduced in females at 200 ppm diet (-6% on lactation days 7-14, -9% on lactation days 14-21)
- Viability index slightly reduced at 200 ppm (96.2% vs. 98.6% in the controls).
- Lactation index significantly decreased at 200 ppm diet (88.6% vs. 94.4% in controls, $p<0.05$) after 21 days lactation.
- Slight increase in pup mortality at 200 ppm diet
- Pup body weights significantly decreased at 200 ppm diet in both sexes after 14 and 21 days lactation (-19 to -21%, $p<0.01$).
- Slight delay in vaginal opening at 200 ppm diet.
- Slight decrease in relative thymus weight in males at 60 ppm diet; significant decrease in relative thymus weight in both sexes at 200 ppm diet.
- Increased incidence of thymic involution at 200 ppm diet (significant for males only) at microscopic examination.

- Functional tests and examination of morphological landmarks revealed no substance-related findings at all dose-levels except for a slightly delayed in vaginal opening at 200 ppm.
- Microscopic examination of the other organs found no substance-related changes.

F1 generation:

- No mortality.
- Body weight: significant reduction in males at 200 ppm diet.
- Food consumption: reduced in females at 200 ppm diet; significant on lactation days 14-21.
- Increased number of stillbirths at 200 ppm diet (26 vs. 5 in controls).
- Viability index: decreased at 200 ppm (82.0% vs. 95.7% in controls).
- Pup mortality: increased at 200 ppm diet from day 4-21 of lactation.
- Lactation index: decreased at 200 ppm diet (82.3% vs. 94.4%).
- Pup body weight: significantly reduced at 200 ppm for males and females on days 4, 7, 14, and 21 of lactation (males pups between approx. 3% and 19%; female pups between approx 4% and 21%, $p<0.01$).
- Morphological changes: pinna unfolding, eye and ear opening were slightly delayed at 200 ppm diet.
- Relative thymus weight: showed a tendency towards a decrease in males and females rats at 60 ppm (in the female statistically significant, at $p<0.05$). and was significantly decreased in both sexes at 200 ppm ($p<0.01$).
- Relative spleen weight: significantly decreased in females at 200 ppm diet.
- Increased incidence of thymic involution at 200 ppm (significant for males) at microscopic examination.

The NOAEL for F0 males and females was 20 ppm diet (approx. 1.5 mg/kg bw/day) based on a slightly reduced relative thymus weight for males at 60 ppm (approx. 4.4 mg/kg bw/day).

The NOAEL for the F1 generation was 20 ppm diet (approx. 1.6 mg/kg bw/day), based on a reduction in relative thymus weights for males and females at 60 ppm diet (approx. 4.7 mg/kg bw/day).

No teratogenic effects were observed in this study.

- In the 13 consecutive weeks study (according OCDE 408 guideline) combined with the reprotox screening assay (according to OECD 421) performed with the hydrolysis product DOTC (Appel and Waalkens, 2004) (purity>94%), comparable effects were observed:

At 10 ppm (equivalent 0.7 mg/kg bw/day for males and 0.5-0.7 mg/kg bw/day for females), treatment-related effects to dams included lymphoid depletion were observed in dams.

At 100 ppm (equivalent to 6.5 mg/kg bw/day for males -6.8 mg/kg bw/day for females, treatment-related effects included increased post-implantation loss (49%), decreased gestation index (71%) decreased live birth index (53%), decreased viability index (74%), increased number of runts, increased pup mortality (PN1 and 4), and decreased absolute and relative thymus weights and lymphoid depletion in the dams.

At 300 ppm (equivalent to 19.3 mg/kg bw/day for males -19.8 mg/kg bw/day for females), treatment-related effects included increased in post-implantation loss (70%), decreased gestation index (50%), decreased live birth index (60%) decreased viability index (12%), increased number of runts, decreased pups weights (PN 1and 4), increased pup mortality (PN 1 and 4), and decreased absolute and relative thymus weights and lymphoid depletion (dams).

Summary of litter data

- Litter size: The mean number of pups delivered per litter amounted to 11.7, 11.0, 10.3 and 8.6 for the control, 10, 100 and 300 ppm groups,respectively.
- Litter weight: Mean pup weights and pup weight changes were similar in the 10 and 100 ppm groups when compared to the control group. Pup weight of the 300 ppm group (PN 1, 3 litters and PN 4, 1 litter) was reduced.
- Pup mortality: 1.4, 4.5, 47 and 40% in the control, 10, 100 and 300 ppm groups, respectively (PN 1); 5.8, 8.3, 26 and 88% in the control, 10, 100 and 300 ppm, respectively (PN 4).
- Number viable: The viability index (PN 1-4) was 94, 92, 74 and 12% in the control, 10, 100 and 300 ppm groups ,respectively.
- Number live pups per litter: 11.5, 10.5, 7.6 and 6.5 for the control, 10, 100 and 300 ppm groups, respectively (PN 1); 10.8, 11.0, 9.3 and 3.0 for the control, 10, 100 and 300 ppm groups, respectively (PN 4).
- Sex ratio: No difference was observed in the sex ratio between the groups.

The above developmental effects were associated with maternal toxicity substantiated by a statistically decrease in absolute and relative thymus weight in the 100 (c. 62 and 67% in male and females,) and 300 ppm group (31 and 38% in males and females)

and a moderate to very severe lymphoid depletion in dams (5/10 animals at 10 ppm and in all animals of the 100 and 300 ppm groups.

Based on reproductive and developmental effects in the screening reprotox assay (particularly severe post-implantation losses and fetal losses) observed after mating of 100 and 300 ppm female of the satellite groups with male animals of the main study, the low dose level of 10 ppm in diet (equivalent to 0.7 mg/ kg bw/day in males and 0.5-0.7 mg/kg bw/day for females) can be considered as a NOAEL for fertility and developmental effects.

Based on the treatment related histological changes in the thymus (lymphoid depletion) of the 10 mg/kg female animals of the satellite groups, 10 ppm in diet (equivalent to 0.5-0.7 mg/kg bw/day) was considered to be a LOAEL for maternal toxicity.

Summary for effects on fertility

Under the experimental conditions of the two generation study on a mixture of Dioctyltin bis(IOMA) and Octyltin tris(IOMA) (78.8:16.9%), the NOAEL for the F0 parental generation was 20 ppm (~1.5 mg/kg bw/day), based on a reduction in the relative thymus weight of males at 60 ppm (~4.7 mg/kg bw/day). The NOAEL for the F1 generation until weaning was 20 ppm (~1.6 mg/kg bw/day), based on a decrease in relative thymus weight in male and female pups at 60 ppm. The NOAEL for the F1 generation post-lactation was 20 ppm, based on a slight decrease in the relative thymus weight of males and an increase in stillbirth at 60 ppm.
Indices of mating, fertility, gestation and the pregnancy rates were within the range of the control group at 20 and 60 ppm. The mean pre-coital time, duration of pregnancy in days and duration in hours did not show any substance related effects at all dose-levels. The fertility index was slightly decreased at 200 ppm but was within the range of historical control data. In addition, the viability and lactation indices were decreased at 200 ppm in both the F0 and F1 generation, this was associated with a decreased in pups body weight (by 3 to 4%) in the F0 generation and a significant decrease in pups weight in the F1 generation (males pups between approx. 3% and 19%; female pups between approx 4% and 21%, at $p<0.01$) during the lactation period.

There is a GLP screening reprotoxicity study according to OECD guideline 421 (Appel and Waalkens, 2004) performed with the hydrolysis product dioctyltin dichloride (3542-36-7) and described in detail in section 7.8.3. In this GLP key study, comparable effects were obtained with the two generation study, indeed thymus effect were also recorded. Dose-related effects were seen at 10, 100 and 300 ppm, with post-implantation losses in the top two dose groups. The maternal LOAEL was set at 10 ppm diet (equivalent 0.7 mg/kg bw/day for males and 0.5-0.7 mg/kg bw/day for females) for treatment related effects to dams included lymphoid depletion.

In the screening reprotoxicity study performed with the hydrolysis product DOTC, no effects were observed on the mating index, the precoital time was comparable for the control and the treated groups, the female fecundity index , female fertility index and male fertility index were not affected while the gestation index was 86, 100, 71 and 50% in the control, 10, 100 and 300 ppm groups, respectively. The livebirth index was 99, 95, 53 and 60% in the control, 10, 100 and 300 ppm groups, respectively. Post-implantation loss was 22.3, 21.0, 49.2 and 70% for the control, 10, 100 and 300 ppm groups, repectively.

Developmental toxicity

1/In the developmental toxicity study in rats (Battenfeld, 1991), dams were treated with mixture of DOT(IOMA) and MOT(IOMA) (80:20%) at 1, 5 and 25 mg/kg bw/day during day 6-15 of gestation.

Maternal effects:

Alopecia was observed in single animals of all four groups and was not attributed to treatment. There was a slight (non significant) decrease in corrected body weight and corrected body weight gain from day 6 to day 21 at 25 mg/kg bw/day dose. This reduction was attributed largely to one single dam (dam No.97).

Fetal observations:

There was a statistically increase in the percentage of dead fetuses at 25 mg/kg bw/day. The seven dead fetuses concerned only on one litter (dam No.97). Though clear-cut effects were found in only one dam in 25 mg/kg bw/day dose group, the test substance was considered to **induce marginal maternal toxicity in one single dam (only a decrease in body weight gain (-58g) in dam No. 97) at** 25 mg/kg bw/day. There were no treatment related malformation or variation at any dose-level.

- The dose-level without maternal and/or embryo-fetotoxicity (embryo-fetal NOAEL and maternal NOAEL) was 5 mg/kg bw/day (equivalent to 0.77 mg Sn/kg bw/day).

- A NOAEL for skeletal malformations and variations was the highest tested dose of 25 mg/kg bw/day.

2/In the mice developmental toxicity study (Faqi, 2001), dams were given mixture (80:20%) of DOT(IOMA) and MOT(IOMA) at 20, 30, 45, 67 and 100 mg/kg bw/day during day 6 to 17 of pregnancy.

Maternal effects:
There was a dose dependent decrease in maternal body weight gain, but differences were not significant in mice exposed to the test substance. No signs of toxicity were observed with the exception of one dam in the 100 mg/kg bw/day dose group that died. Pregnancy rates were comparable between treated groups and the control groups.
The mean maternal thymus weights in the 45 and 100 mg/kg bw/day dose groups were significantly lower than the control groups (-27%, $p<0.05$ at 100 mg/kg bw/day). At 67 mg/kg bw/day, the mean maternal weight was slightly but not significantly decreased. Maternal liver weights were significantly lower in the 100 mg/kg bw/day dose group (-23 %, $p<0.05$ at 100 mg/kg bw/day). The number of implantations per litter was comparable between treated groups and the control groups. Resorption rates were significantly increased in mice treated with 67 or 100 mg/kg bw/day.

Fetal observations:

Fetal weights were significantly decreased in the 67 and 100 mg/kg bw/day groups. There were no dead fetuses in any of the treated groups. There were no external malformations reported in the fetuses exposed to 20, 30, or 45 mg/kg bw/day, however a significantly increased incidence of cleft palate in the fetuses exposed to 67 or 100 mg/kg bw/day were observed, and incidences of bent forelimbs and exencephaly were significant in the fetuses exposed to 100 mg/kg bw/day. Skeletal variations reported in the low dose groups included unossified digit and supernumerary cervical ribs (significantly increased at 20 and 45 mg/kg bw/day, but not at 30 mg/kg bw/day); hindpaw incompletely ossified, Os frontale misshapened, and interparietale incompletely ossified (significantly increased at 45 mg/kg bw/day); and supernumerary lumbar or cervical ribs (significantly increased at 20, 30, and/or 45 mg/kg bw/day). There was a significant increase in skeletal abnormalities in the fetuses of dams exposed to 67 or 100 mg/kg bw/day. Skeletal abnormalities reported in these dose groups included bent forelimbs, bent hindlimbs, dislocated sternum, fused or bent ribs, or bent vertebral column. Skeletal variations were observed in the low dose groups (20, 30, or 45 mg/kg bw/day).
The authors defined malformations as a permanent or irreversible structural change that is likely to adversely affect survival or health. The authors reported a no-observed-adverse-effect-level (NOAEL) for each endpoint examined, i. e., malformations, variations, organ toxicity.

- The embryo-fetal NOAEL for malformations was reported as 45 mg/kg bw/day, based on an increased incidence of cleft palate in fetuses from dams exposed to 67 mg/kg bw/day.
- A NOAEL for skeletal variations could not be determined, but would be expected to be < 20 mg/kg bw/day, based on an increased incidence of supernumerary lumbar ribs observed at 20 mg/kg bw/day.
- The authors reported that the NOAEL for maternal organ toxicity was 30 mg/kg bw/day, based on a significant decrease in thymus weight at 45 mg/kg bw/day.

3/In the rabbit developmental toxicity study (Battenfeld, 1992), dams were given mixture of DOT(IOMA) and MOT(IOMA) (80:20%) during day 6-18 of pregnancy at 1, 10 and 100 mg/kg bw/day.

Maternal effects:
Except for a nasal hemorrhage in one dam of Group 2 (1 mg/kg bw/day), slight torticollis in one dam of Group 3 (10 mg/kg bw/day), and bloody outflow in 3 dams of Group 4 (100 mg/kg bw/day), no clinical observations were made. In total, 18 of 24 dams in Group 1, 23/23 in Group 2, 18/22 in Group 3, and 17/24 in Group 4 survived until day 28. Two dams in Group 1 and 3 dams in Group 3 died after treatment had commenced. Death resulted from infectious diseases (pneumonia or enteritis), and there was no dose-related increase. Therefore, these deaths were not attributed to the test substance. In Group 1, 3 dams were eliminated because of normal deliveries before day 28. Before start of treatment, one dam in Group 1 and one dam in Group 2 were found dead. Maternal body weight data did not reveal differences between treatment groups. Abortion was diagnosed in one dam of Group 1 and 4 dams of Group 4. All abortions occurred after termination of treatment. The high incidence of abortion in Group 4 was considered to result "at least partly from a slight maternal toxic effect of the test compound."

Fetal observation:
Total fetal death was found only in Groups 1 and 4. In both groups, total post-implantational loss occurred in 3 dams. Percentages of post-implantation losses per group were 17.7% (control), 10.5 % (1 mg/kg bw/day), 5.7% (10 mg/kg bw/day), and 28.4%, $p<0.05$ (100 mg/kg bw/day). The significant increase in post-implantation loss at the high dose-levels was explained by a significant increase of total resorptions (28.4 %, $p<0.05$ vs. 17.1% in controls).
External examination revealed two nasal clefts and an encephalocele in one fetus of group 2. Umbilical hernia was found in one fetus of the control group and in one fetus each in Groups 3 and 4. These were not associated with treatment. Other

findings, such as malformations of the vertebral column (one animal in Group 4) and absence of the right kidney and adrenal gland (one animal in Group 4) were regarded as chance findings and not attributed to treatment due to their single occurrence and because they represented totally different types of malformations. The lack of a statistically significant difference to the control group and inconsistency regarding the type of anomaly found did not "point towards a compound-related effect." Fetuses with minor external anomalies (flexion of digits and limbs, open eyelids, shortened tail) were observed in all four groups, and not attributed to the test substance. Minor visceral anomalies found included severely dilated renal pelves and additional small vessels originating from the aortic arch. The statistically significant increase in the incidence of visceral anomalies of fetuses in Group 4 is an indication of retardation in fetal development. Individual body weights of the fetuses in Group 4 with minor visceral anomalies were approximately 40% lower than the mean weight of control fetuses. Suspected or definite compound-related changes noted included:
-1 mg/kg bw/day: No substance-related effects.
-10 mg/kg bw/day: Slight non-significant increase in minor skeletal head anomalies (incompletely ossified bones in the skull).
-100 mg/kg bw/day: clear substance-related embryotoxic effects were noted i. e. significantly increased incidence of abortions, post-implantation loss, minor visceral anomalies (severely dilated renal pelves and additional small vessels originating from the aortic arch), minor skeletal head anomalies (incompletely ossified bones in the skull), and skeletal variations of the sternum and feet bones (not or incompletely ossified sternebrae and feet bones); and a significant reduction in fetal body weight.

In conclusion, the author of the rabbit developmental toxicity study reported that the evaluation of reproduction data and fetal weights indicated a slight embyrolethal and moderate retardative effect (with regard to fetal development) at the high dose level (100 mg/kg bw/day) associated with maternal toxicity (abortions)).

5/Two generation study performed under GLP and according to OECD 416 with a mixture of Dioctyltin bis(IOMA) Octyltin tris(IOMA) (Anonymous, 1997)

Please refer to section effects on fertility for details**.**
The NOAEL for F0 males and females was 20 ppm diet (approx. 1.5 mg/kg bw/day) based on a slightly reduced relative thymus weight for males at 60 ppm (approx. 4.4 mg/kg bw/day).

The NOAEL for the F1 generation was 20 ppm diet (approx. 1.6 mg/kg bw/day), based on a reduction in relative thymus weights for males and females at 60 ppm diet (approx. 4.7 mg/kg bw/day).

No teratogenic effects were observed in this study.

6/Screening reprotoxic assay performed under GLP and according to OECD 421) with the hydrolysis product DOTC (Appel and Waalkens, 2004)

Please refer to section effects on fertility for details**.**
Based on reproductive and developmental effects in the screening reprotox assay (particularly severe post-implantation losses and fetal losses) observed after mating of 100 and 300 ppm female of the satellite groups with male animals of the main study, the low dose level of 10 ppm in diet (equivalent to 0.7 mg/kg bw/day in males and 0.5-0.7 mg/kg bw/day for females) can be considered as a NOAEL for fertility and developmental effects.

Based on the treatment related histological changes in the thymus (lymphoid depletion) of the 10 ppm female animals of the satellite groups, 10 ppm in diet (equivalent to 0.5-0.7 mg/kg bw/day) was considered to be a LOAEL for maternal toxicity.

To assess teratogenic effects was not subject of this study. Thus, the animals were not in deep examined regarding external, soft tissue or skeletal abnormatities. However, grossly visible abnormalities were recordet.

Summary for developmental toxicity

A two generation study and developmental toxicity studies in mice, rats and rabbits with mixed DOT(IOMA):MOT(IOMA) (78.8:16.9, 80:20 ratio) showed maternal effects on the thymus, dose-related retardations and variations in mice and rabbits, increased post-implantation losses, and decreased fetal weight plus decreased fetal viability in mice and rabbits. Compared to the screening study with DOTC, it can be concluded that in the comparable period of pregnancy, the effects on fetal weight and viability were basically the same. In contrast, rats did not show any variations of bone formation seen in mice and rabbits.
Serious skeletal malformations (bent forelimbs, bent hindlimbs, dislocated sternum, fused or bent ribs and bent vertebral column) are seen in mice only at the maternal toxic doses of 67 and 100 mg/kg bw/day.

From the three developmental studies in rat, mice and rabbits the following NOAEL could be derived:

The NOAEL for maternal toxicity and embryofetal development in the rat study were set at 5 mg/kg bw/day (based on decrease in maternal body weight gain and increase in the percentage of dead fetuses at 25 mg/kg bw/day). The NOAEL for skeletal

malformations and variations was the highest tested dose of 25 mg/kg bw/day.

In the mice study, the embryofetal NOAEL for malformations was reported at 45 mg/kg bw/day based on an increased incidence of clef palate in fetuses from dams given 67 mg/kg bw/day. A NOAEL for skeletal variations could not be determined, but would be expected to be <20 mg/kg bw/day, based on an increased incidence of supernumerary lumbar ribs observed at 20 mg/kg bw/day. The NOAEL for maternal organ toxicity was 30 mg/kg bw/day, based on a significant decrease in thymus weight at 45 mg/kg bw/day.

In the rabbit study, the NOAEL for developmental and maternal toxicity was set at 10 mg/kg bw/day The evaluation of reproduction data and fetal development indicated a slight embryofetal and moderate retardative effect at 100 mg/kg bw/day (significantly increased incidence of abortion, increase incidence of post-implantation losses, increased incidence of external and visceral malformation) while maternal toxicity was very slight.

In the two generation study reported above (Anonymous,, 1997), immune effects were observed in the F0 and F1 progeny as shown by the decreased in the relative thymus weight from 60 ppm (approx. 4.7 mg/kg bw/day). In addition, the viability index was markedly decreased and the pup weight was significantly decreased at 200 ppm in both F0 and F1 generation.

It important to highlight that the skeletal fetal malformation observed in mice (bent forlimbs, bent hindlimb, dislocated sternum, fused or bent ribs and bent vertebral (column) and in rabbits (not or incompletely ossified sternebrae and feet bones) were not observed in rats. Furthermore, these fetal observations occur at dose-levels where the maternal animals showed always slight to moderate maternal toxicity.

Toxicity to reproduction: other studies

The gastric hydrolysis rates support the conclusion that dioctyltin dichloride (DOTC) (Cas No. 3542-36-7) is the toxophore in the oral studies, due to rapid gastric hydrolysis of the dioctyltin thioglycolate ester to the chloride. DOT(IOMA) (Cas No 26401-97-8) is an isomer of (DOT(2-EHMA) (CAS No. 15571-58-1) that is considered to behave similarly.

The lowest NOAEL (actually 0.5-0.7 mg/kg bw/day) was found in the combined repeated dose and reproduction/developmental toxicity test with DOTC (Apple and Waalkens, 2004). At the higher dose levels effects on pups such as increase in number of runts, increased number of cold pups, number of pups per litter, were observed. Based on the observed histological changes in the thymus (lymphoid depletion) of the 10 ppm in diet females, the low dose of 10 ppm in diet (equivalent to 0.5-0.7 mg/kg bw/day for females) was considered to be a LOAEL for maternal toxicity.

Imunotoxicity study of prenatal rat exposure (Smialowicz, 1988)
Fisher rats were exposed prenatally, both pre and post-natally, or post-natally to DOTC by oral gavage of pregnant and/or lacatating females. At various ages, ranging from 3 to 16 weeks of age, offspring were examined for a number of immune functions. These included body and lymphoid organ weights; lymphoproliferative responses to B and T-cell mitogens; natural killer cell activity; an preimary antibody response to sheep erythrocytes. Prenatal (10-20 of gestation), pre and post-natal (d 11-20 of gestation and 2-11 d of age), or post-natal (2-13 d of age) oral dosing of dams with 20-50 mg DOTC/kg bw/day resulted in no consistent alteration in immune function in offspring. However, direct oral dosing of rat pups to 5-15 mg DOTC/kg bw/day, beginning at 3 d of age and then 3 times per week up to 24 d of age for a total of 10 doses, resulted in significant suppression of the lymphoproliferative response of splenocyte to a T-cell mitogen in 10 week old rats (i.e. 7 week after the last exposure to DOTC). Lymphoproliferative responses returned to control levels by 12 weeks of age. In comparison, young adults (8 week old) rats dosed with 10 or 20 mg DOTC/kg bw/day under an identical dosing schedule (i.e., 3 times per week for a total of 10 doses) showed no suppression in the mitogen response of splenocytes 4 week after the last exposure to DOTC. These results suggest that direct dosing of pups during early post-natal life may be the most effective means of inducing immunosuppression with DOTC during immune system development.

4.11.5 Comparison with criteria

There were relevant observed developmental effects in the two generation study performed with DOT(IOMA): MOT(IOMA) (78.8: 16.9%) and in the developmental reprotoxicity studies with DOT(IOMA): MOT(IOMA) 80:20%, particularly the effects on pups such as increased in number of runts, decreased fetal weight, decreased number of pups per litter, increased post-implantation loss, decrease thymus weight for the F0 parent and F1 progeny from 60 ppm in diet (approx. 4.7 mg/kg bw/day).
In addition, the screening reprotoxicity feeding study with the hydrolysis product DOTC support also a part of these particular findings (increase post-implantation loss, decreased viability index, increase number of runts, decreased pups weights) associated with maternal toxicity substantiated by a statistically decrease in absolute and relative thymus weight in the 100 (c.

62 and 67% in male and females,) and 300 ppm in diet group (31 and 38% in males and females) and a moderate to very severe lymphoid depletion in dams (5/10 animals at 10 ppm in diet and in all animals of the 100 and 300 ppm in diet.

Based on the reproductive and developmental effects in the screening reprotox assay (particularly severe post-implantation losses and fetal losses) observed after mating of the 100 and 300 ppm females of the satellite groups with male animals of the main study, the low dose level of 10 ppm in diet (equivalent to 0.7 mg/kg bw/day in males and 0.5-0.7 mg/kg bw/day for females) can be considered as a NOAEL for fertility and developmental effects.
Based on the treatment related histological changes in the thymus (lymphoid depletion) of the 10 ppm female animals of the satellite groups, 10 ppm in diet (equivalent to 0.5-0.7 mg/kg bw/day) was considered to be a LOAEL for maternal toxicity.

The developmental studies reported an increased incidence of abortions, post-implantation losses and marked retardations of fetal development in the rabbits at 100 mg/kg bw/day and a dose-related increase incidence of resorptions and of external fetal malformation in the mice from 67 mg/kg bw/day.

The above reported effects (increased post-implantation loss, increase incidence of resorption, increase pups mortality, depressed fetal weight) are indicative of developmental effects. These effects observed in all the above reported studies were almost always associated with moderate maternal toxicity (substantiated most of the time by a significant thymotoxicity characterized by a decreased in thymus weight and by a moderate to severe lymphoid depletion at microscopic examination), which may indicate that they could have been secondary effects to maternal toxicity.
It is well-known that the thymus which is reported to have a crucial role during pregnancy (Clarke et al., 1994) is the target organ of organotins (Gennari publications). Although the mechanism of action of thymus involution on embryo development is still unclear, it could be considered as a secondary specific maternally-mediated mechanism which is, according to CLP criteria, correspond to a classification in category 2 for reproductive toxicity.

In addition, the fact that all these studies were performed with either the hydrolysis product or the isomers of the DOT(2-EHMA) make the quality of evidence less convincing as they were not performed on the substance it self, which is again ,according to CLP criteria correspond to a classification in category 2 for reproductive toxicity.

Moreover, impurities (as described in Chapter 4.7.1.7) are known to be present in the tested DOT substances and may have contributed to the observed effects. The degree of this contribution should be investigated.

Based on these elements, DOT(2 -EHMA) is proposed to be classified with R63: 'Possible risk of harm to the unborn child' according to Directive 67/548/EEC and 'Reprotoxicity category 2', H361d according to CLP.

4.11.6 Conclusions on classification and labelling

Directive 67/548/EEC	CLP
Reprotoxicity category 3 R63: possible risk of harm to the unborn child	Reprotoxicity category 2 H361d: Suspected of damaging the unborn child

4.12 Other effects

No data is available.

5 ENVIRONMENTAL HAZARD ASSESSMENT

Not evaluated in this dossier.

6 OTHER INFORMATION

Not relevant.

7 REFERENCES

Anonymous (1970). Subchronic (90-day) toxicity studies with two organic tin compounds (Advastab 17 MOK 034 and Advastab 17 MOK 028) in albino rats. Testing laboratory: CIBA-GEIGY Corporation. Report no.: 88-920001834. Owner company: Crompton GmbH. Report date: 1970-01-01.

Anonymous (1974). 90-day dietary study in rats with compound TK 10 315. Testing laboratory: CIBA-GEIGY Ltd. Owner company: Crompton GmbH. Report date: 1974-11-06.

Anonymous (1978a). Mutagenicity Evaluation of Irgastab 17 MOK in the Ames Salmonella/Microsome Plate Test. Testing laboratory: Litton Bionetics, Inc. Report no.: LBI Project No. 20998. Owner company: Crompton GmbH. Report date: 1978-12-01.

Anonymous (1978b). Mutagenicity Evaluation of Irgastab 17 MOK in the Ames Salmonella/Microsome Plate Test. Report no.: LBI Project No. 20998. Owner company: Crompton GmbH. Report date: 1978-12-01.

Anonymous (1979). Salmonella/Mammalian-Microsome Mutagenicity Test with TK10 315. Testing laboratory: CIBA-GEIGY Ltd. Report no.: 78/2657. Owner company: Crompton GmbH. Report date: 1979-08-28.

Anonymous (1983). Salmonella/Mammalian-Microsome Mutagenicity Test. Test Material: TK 10 315 (Irgastab 17 MOK). Testing laboratory: CIBA-GEIGY Ltd. Owner company: Crompton GmbH. Study number: Project No. 830541. Report date: 1983-09-15.

Anonymous (1992a). Acute Oral Toxicity in the Rat. TK 10315 (Irgastab 17 MOK). Testing laboratory: CIBA-GEIGY Ltd. Report no.: 924128. Owner company: Crompton GmbH. Report date: 1992-11-02.

Anonymous (1992b). Acute Dermal Toxicity in the Rat. TK 10315 (Irgastab 17 MOK). Testing laboratory: CIBA-GEIGY Ltd. Owner company: Crompton GmbH. Study number: Test No. 924129. Report date: 1992-10-14.

Anonymous (1992c). Acute Dermal Irritation/Corrosion Study in the Rabbit. TK 10315/A (Irgastab 17 MOK-A). Testing laboratory: CIBA-GEIGY Ltd. Owner company: Crompton GmbH. Study number: Test No. 924131. Report date: 1992-11-10.

Anonymous (1993a). Skin Sensitization Test in the Guinea Pig Maximization Test. TK 10315/A (Irgastab 17 MOK-A). Testing laboratory: Ciba-Geigy Ltd. Report no.: 924133. Owner company: Crompton GmbH. Report date: 1993-01-28.

Anonymous (1993b). Skin sensitisation test in the guinea pig Maximisation Test. TK 10315 (Irgastab 17 MOK). Testing laboratory: CIBA-GEIGY Ltd. Report no.: 924130. Owner company: Crompton GmbH. Report date: 1993-02-02.

Anonymous (1997). Two-generation reproduction toxicity study of MOTTG/DOTTG in rats by administration in the diet. Testing laboratory: LPT Laboratory of Pharmacology and Toxicology, Redderweg 8, D-21147 Hamburg. Report no.: LPT Report No. 6247/1/91. Owner company: Crompton GmbH. Report date: 1997-03-05.

Appel, M. J. and D. H. Waalkens-Berendsen. (2004). Dichlorodioctylstannane [CASRN # 3542-36-7]: Sub-chronic (13 week) oral toxicity study in rats, including a reproduction/developmental screening study. Testing laboratory: TNO Nutrition and Food Research. Report no.: V3964, April 2004. Owner company: ORTEP ASSOCIATION. Report date: 2004-05-27.

Auletta, C. S. and Daly, I. W. (1984). Acute oral toxicity study in rats. Testing laboratory: Biodynamics, Inc. Report no.: 5108-84. Owner company: M&T Chemicals, Inc., P. O. Box 1004, Rahway, New Jersey, 07065, USA. Report date: 1984-11-08.

Baltussen E (2010). Determination of physico-chemical properties of dioctylin bis(2-ethylhexylmercaptroacetate). Testing laboratory: NOTOX B. V., Hambakenwetering 7, 5231 DD 'S-Hertogenbosch, The Netherlands. Report no.: 492799. Owner company: ReachCentrum SPRL; Organo Tin REACH Consortium, Avenue Edmond van Nieuwenhuyse 6, 1160 BRUSSELS, Belgium. Report date: 2010-05-20.

Battenfeld, R. (1991). Embryotoxicity including teratogenicity study in the rat after daily intragastric administration from day 6 to day 15 of gestation. Testing laboratory: Schering AG. Report no.: IC 18/90, ZK 30.434. Owner company: Crompton GmbH. Report date: 1991-07-25.

Battenfeld, R. (1992). Embryotoxicity including teratogenicity study in the rabbit after daily intragastric administration from day 6 to day 18 of gestation. Testing laboratory: Schering AG. Report no.: IC 14/90, ZK 30.434. Owner company: Crompton GmbH. Report date: 1992-03-02.

CIBA-GEIGY Ltd. (1992). Acute Dermal Toxicity in the Rat. TK 10315 (Irgastab 17 MOK). Testing laboratory: CIBA-GEIGY Ltd. Owner company: Crompton GmbH. Study number: Test No. 924129. Report date: 1992-10-14.

Clarke (1994). The thymus in pregnancy: the interplay of neural, endocrine and immune influences. Immunology today. Vol 15. No. 11 1994.

Faqi, A. S., H. Schweinfurth, and I. Chahoud (2001). Developmental toxicity of an octyltin stabilizer in NMRI mice. Reproductive Toxicology. 15:117-122.

Hossack D. J. N, Richold, M. and Richardson, J. C. (1980). Micronucleus test on ZK 30 434. Testing laboratory: Huntingdon Research Centre, Huntingdon, Cambridgeshire, UK. Report no.: SHG 182/79184. Owner company: Schering A. G., D-1 Berlin 65, Postfach 65 03 11, Germany. Report date: 1980-01-22.

Kim J (2004). Benchmark dose analysis for dioctyltin dichloride (CAS 3542-36-7). Testing laboratory: Sciences International Inc. Report no.: Project Number 1502. Report date: 2004-04-21.

Krul, C. A. M. (2003). Dichlorodioctylstannane [CAS# 3542-36-7]: Micronucleus test in rat bone marrow cells. Testing laboratory: TNO Chemistry, Department of Biomolecular Sciences, 3700 AJ Zeist, The Netherlands. Report no.: V3404/14. Owner company: ORTEP. Report date: 2003-03-04.

ORTEP Association Stabilizer Task Force (2000). Summary Report - The Simulated Gastric Hydrolysis of Tin Mercaptide Stabilizers. Owner company: ORTEP Association Stabilizer Task Force. Report date: 2000-05-01.

Pelikan, Z. and E. Cerny (1970). The toxic effects of some di- and mono-n-octyl-tin compounds on white mice. Arch. Toxikol. 26:196-202.

Steenwinkel MJST, and Van der Horst-Groeneveld JML. (2010). Gene mutation test at the TK-locus of L5178Y cells with Dioctyltin bis(2-ethylhexylmercaptoacetate). Testing laboratory: TNO Quality of Life, Utrechtseweg 48, PO Box 360, 3700 AJ Zeist, The Netherlands. Report no.: V8403/12 (TNO study code: 8403/12). Owner company: ReachCentrum SPRL for account of the members of the organoTin reach consortium. Report date: 2010-04-12.

Varsho B. J. (1996). Primary dermal irritation study of dioctyltin bis (2-ethyl-hexylmercaptoacetate) in albino rabbits. WIL Research. Testing laboratory: WIL Research Laboratories, Inc. Report no.: WIL-160060. Owner company: Elf Atochem North America, Inc. Study number: WIL-160060.

Varsho, B. J. (1996). Primary Eye Irritation Study of Dioctyltin bis(2-ethyl-hexylmercaptoacetate) in Albino Rabbits. Testing laboratory: WIL Research Laboratories Inc., 1407 George Road, Ashland, Ohio, 44805-9281, USA. Report no.: WIL-160061. Owner company: Elf Atochem North America, Inc., 2000 Market Street, Philadelphia, Pennsylvani, 19103, USA. Report date: 1996-10-09.

Ward, R. J. (2003). Dioctyltin bis(2-ethylhexylmercaptoacetate): In vitro absorption through human and rat epidermis. Testing laboratory: Central Toxicology Laboratory. Report no.: CTL/JV1701/Regulatory/Report. Owner company: Tin Stabilizer Association. Report date: 2003-01-08.

Yoder, R. (2003). Electrospray Ionization Mass Spectrometric Study of Dioctyltin Compounds in Solution. Testing laboratory: not reported. Report no.: not reported. Owner company: Arkema. Report date: 2003-05-01.

Yoder R. (2000). Measurement of the hydrolysis of various organotin stabilizers under simulated gastric conditions. Ortep report. May 15.