ECHA
European Chemicals Agency

Committee for Risk Assessment
RAC

Annex 2

Response to comments document (RCOM)
to the Opinion proposing harmonised classification and labelling at Community level of
TDCP
ECHA/RAC/CLH-0-0000000953-71-03/A2

Adopted
3 September 2010

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Substance name: TDCP (Tris[2-chloro-1-(chloromethyl)ethyl] phosphate)
CAS number: 13674-87-8
EC number: 237-159-2

General comments

Date	Country/ Person/Organisation/ MSCA	Comment	Response	RAC Rapporteur's comment
2009/10/06	Germany / TDCP consortium	The Annex XV report from Ireland is an accurate reflection on what has been agreed in the risk assessment carried out in the framework of Council Regulation (EEC) No. 793/93 and recently published. The outcome and conclusions from the risk assessment process especially regarding the carcinogenicity and fertility endpoints are fully covered by the Annex VI report, and were established after exhaustive debates between experts, member states representatives, industry and rapporteur. Therefore, industry supports the conclusions in the above mentioned report. In addition, industry had already taken the initiative (in compliance with Directive 67/548 on classification & labelling) to self-classify and label this product with R40, "limited evidence of a carcinogenic effects" many years ago, which followed directly from the results of the 2 year oral carcinogenicity study done by industry on TDCP in 1981. This decision is now being confirmed by the Annex VI dossier.	Thank you for your comment.	*Through these two comments rapporteur and corapporteur notice the support of the TDCP consortium to the C3 / R40 (C2/H351) proposal of Ireland.*

Date	Country/ Person/Organisation/ MSCA	Comment	Response	RAC Rapporteur's comment
		Yours truly, The TDCP industry consortium		
2009/10/06	Germany / Bernd Niederstraßer / MSCA	The German CA is of the following opinion: An interlinkage of neoplastic, non-neoplastic and gonadal effects is discussed in the report. Thus a comparison of the dose-response-relationships of neoplastic, non-neoplastic and gonadal effects is needed to judge on the appropriate classification. To facilitate this a comparing dose-response-table of the different endpoints including the incidences of effects would be very helpful. Repeated dose toxicity is only partly adressed in the report, but a clearer view on this endpoint is important to understand the underlying mechanism of tumor development and gonadal effects. In the report it is sometimes stated, that "Effects were noted … in all animals at 24 months". It should be made clear, whether effects really occurred in all animals or in all groups, what is a difference.	We have included a table of the neoplastic and non-neoplastic effects in the male reproductive organs in section 6.9.1 of the Background Document. Further details on repeated dose toxicity, taken from the 2 year carcinogenicity study, have been included in section 6.6 of the Background document. We have tried to clarify where effects were observed in all animals (i.e. control and treated groups) versus only treated groups.	*1) Rapporteur and Corapporteur also notice the need to better indentify the different forms of neoplasia and to summarise the data; the table proposed by Ireland in section 6.9.1 is the right answer to this request. Rapporteur and corapporteur would have also expected such a table in the carcinogenic section to summarise the effects on weights compared to the carcinogenic observations in the different organs (kidney, liver, testes and adrenal glands) among which kidneys drive the NOAEL. Especially as this way of presenting the date is also important for the discussion of the possible classification on male reproduction toxicity.* *2) This request is in line with the additional table wished by Rapporteur and Corapporteur. Ireland differentiated in its new version the control and treated groups making the information about general toxicity more useable.*

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Carcinogenicity

Date	Country/ Person/Organisation/ MSCA	Comment	Response	*Rapporteur's comment*
2009/10/05	Hungary / Zsuzsanna Kiss / National Institute of Chemical Safety	On the basis of the detailed information on mutagenicity and carcinogenicity tests, we agree with the following (Directive 67/548/EEC) classification: Carcinogen Category 3, R40. In the presence of metabolic activation TDCP was mutagenic in bacterial as well as in lymphoma systems. In a 2 yrs in vivo study tumors were detected in the treated group. In contrary, no human tumors were found in the cohort study cited, so no higher classification is reasonable.	Thank you for your comment.	*Rapporteur and corapporteur note here again a support to Ireland's proposal. Here also some mutagenicity results were considered as an argument for the carcinogen classification; this consolidates the choice of Rapporteur and Corapporteur to also discuss a little the mutagenicity endpoint and the absence of human data to argue no higher category classification for carcinogenicity.*
2009/10/06	Germany / Bernd Niederstraßer / MSCA	The German CA is of the following opinion: Increased incidences of benign tumors were observed in the kidney, liver, testes and adrenal glands. Increased incidences of malignant tumors were observed in the liver. The dossier would benefit from more information on historical control data and the statistical significance of hepatocellular carcinomas.	The carcinogenicity study was performed in 1981 and as stated in the Annex VI report, all information from the study could not be located and so was not available to us when preparing the dossier. Therefore, we have included all information available. The limited reporting makes statistical analysis of the data difficult. However, we	*Rapporteur and corapporteur agree about the interest of historical control and thank Ireland for its effort to provide some data; and Rapporteur and Corapporteur think that this information wouldn't change the issue of the dossier as several results of the study are still significant (see Rapp table) and also because several organs are of concern.*

[1] Giknis, MLA., Clifford, CB (2001) Compilation of Spontaneous Neoplastic Lesions and Survival in Crl:CD(SD) BR Rats. March 2001. Charles River Laboratories. Available at: http://www.criver.com/SiteCollectionDocuments/rm_rm_r_lesions_survival_crlcd-sd_br_rats.pdf

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		Because of missing in vivo genotoxicity in 5 studies, the proposal to classify as Category 2 Carcinogen with hazard statement H351 is supported.	have obtained historical control data for Crl:CD (SD) BR rats from 24 studies conducted between 1991 and 1997 (Giknis & Clifford, 2001[1]). This was the closest match to the available carcinogenicity study. Giknis & Clifford report the incidence of hepatocellular carcinomas in the historical controls, as percentage of total number of livers examined at 104 weeks, as 2.09 % (min 0.77%, max, 6.67 %) for males and 0.4% (min 0.77%, max 1.67 %) for females. Although statistical significance was not achieved for this lesion in the carcinogenicity study for TDCP, the historical data would support the biological significance. Giknis & Clifford report the incidence of benign interstitial cell tumours in the historical controls, as percentage of total number of testes examined at 104 weeks, as 2.4% (min 1.4%, max 7.14%). It is difficult to interpret this data in the context of the carcinogenicity study for TDCP given the high number of tumours in the concurrent control group (16.3%) at 24 months. However, the statistical and biological significance of the interstitial cell tumours observed in the mid and high dose groups was demonstrated in the TDCP study. As discussed in the Annex VI report, although a significant increase in tumour incidence was observed in the study, TDCP is clearly not genotoxic in vivo and	*Rapporteur and corapporteur agree with the German CA comment and would like to highlight that the significance of hepatocellular carcinomas versus repeated dose toxicity discussion would have been welcomed notably on the side of Freundenthal position paper rather in favour of a toxic effect.*

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			therefore Cat 3 R40 (Cat 2 H351) is supported.	
2009/10/14	Sweden / Swedish Chemicals Agency	We support the Irish proposal concerning carcinogenicity.	Thank you for your comment.	*This is the third support to Irish's proposal.*

Mutagenicity

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
2009/10/06	Germany / Bernd Niederstraßer / MSCA	The German CA is of the following opinion: Because of missing in vivo genotoxicity it is supported not to classify	Thank you for your comment.	*This is the fourth support to Irish proposal: The absence of some genotoxicity positive results is again an argument not to classify in an upper carcinogen category.*

Toxicity to reproduction

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
2009/10/06	Germany / Bernd Niederstraßer / MSCA	Fertility	Before addressing the specific comments raised, we would like to point out a number of issues which should be considered when evaluating the data on the male reproductive organs from the 2 year carcinogenicity study: • The primary aim of the study was to investigate carcinogenicity rather than fertility. Therefore, there are very limited data available for male reproductive organs at 12 months and this makes evaluating the data at 12 months versus that at 24 months	*Taking into account these comments and those from Sweden the available information has been assessed. The comparison of the relevant TDCP data with the classification criteria leads RAC to the conclusion that there is insufficient evidence for classification of TDCP as a male reproductive toxicant.*

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			difficult. We have included a summary table of effects in the Background Document to clarify this point. • As indicated in both the Annex VI report and the Background Document, the reporting of the study is somewhat limited, thus further making evaluation of the data difficult. All information available to us was included in the Annex VI report and is now in the Background Document.	
		The German CA is of the following opinion: Two aspects of the rationale that are presented in the dossier are not fully clear and should be reconsidered: 1: The rapporteur develops the thesis that Leydig-cell-tumors are the cause of non-neoplastic effects in the male gonads. This implies that incidences of non-neoplastic effects cannot be higher than those of Leydig-cell-tumours (control: 16%, low dose: 17%, middle dose: 49%, high dose: 80%). However this is not the situation for all non-neoplastic effects. For example, a reduced secretory product was observed with incidences of 2%, 84%, 89% and 52%. Atrophy of the seminal vesicles showed incidences of 0%, 30%, 31%, 23%. Furthermore in the testis amorphous eosinophilc material in the tubular lumen and periarteritis nodosa were detected in the low dose clearly differing from controls, but tumor	1. We agree there are some effects seen at 24 months in the seminal vesicles and testes in the low dose group, which do not match the Leydig cell tumour incidence in this group at the same time point. We have indicated in the Annex VI report that it is "possible" that the effects observed on the testes may be secondary to an effect of the Leydig cell tumours and therefore this is intended only to be a possibility rather than a definitive mechanism. Therefore, we have amended the Background document to detail the limitations in this theory. Due to the limitation of reporting of data from the 12 month assessment, it is not possible to evaluate whether there is a specific association between non-	

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		incidences were not increased significantly in the low dose. So, the thesis of tumors being exclusively responsible for non-neoplastic effects in male gonads is not sufficiently substantiated.	neoplastic effects in the male reproductive organs and Leydig cell tumours observed at this time point. It should also be noted that the evaluation of the seminal vesicles at 24 months did not include all animals in the low and mid dose groups (13 in low and 19 in mid, compared with 41 in the control and 42 in the high dose). The study report does not indicate why all animals were not evaluated for the low and mid dose or why these specific animals were chosen. Therefore, although there is an increased incidence of decreased secretory product and atrophy of seminal vesicles in all dose groups at 24 months, it is possible that the results for the low and mid doses are skewed due to the low number of animals evaluated.	
		Are there other substances that have a similar mechanism as postulated by the rapporteur?	As indicated in section 6.9.4 of the Background Document, a comparison with either of the structurally similar substances, TCEP or TCPP, is not considered appropriate due to inconsistent effects on male fertility between these substances. In addition, in 2 year carcinogenicity studies in rats and mice with TCEP, no Leydig cell tumours in the male reproductive organs were found. No carcinogenicity data are available for the other structurally similar substance, TCPP.	
		2: In the dossier it is expressed that	2. We accept that effects seen in the latter	

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		gonadal effects which are only observed after 24 months are natural ageing. Natural ageing is what we see after 24 months in the controls. If there is a significant difference between dosed animals and control animals there is something more but natural ageing. Significant effects that only occur in a later period of lifetime are considered to be of lower importance compared to those that become apparent already after 4 weeks or 3 months, but they should not be considered as irrelevant.	period of the study may be secondary to the natural aging process and we had included this statement in the Annex VI report (and the Background document) to highlight the limitations of the data at 24 months rather than to negate them. We acknowledge that there is a higher incidence of some effects on male reproductive organs in the treated groups at 24 months when compared with controls, indicating that some effects may not be due to the aging process alone. However, the influence of non-specific toxicity in these animals also cannot be excluded. Again it should be considered that aging animals are not the ideal population to study effects on fertility. It could be expected that if TDCP has a direct effect on male fertility, such an effect would be observed in the first 12 months of the study. While the limited and poorly reported data from the 12 month observation is difficult to interpret, it does not provide any indication of a direct effect on male fertility.	
		Furthermore it should be made clear whether the dose of 80 mg/kg/d is already in a MTD-range (e g reduced body weight gain) that induces a general toxicity possibly affecting also the gonads by a non-specific mechanism. This would be of interest reflecting on the effects at 80 mg/kg/d. Nevertheless gonadal effects	As stated in section 5.8.6 of the Annex VI report, at the high dose of 80 mg/kg, the terminal body weights were >20% lower than control animals indicating that at this dose the MTD was exceeded. We have clarified this in section 6.9.1 of the Background document.	

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		were already observed in the middle and low dose. Gonadal effects in rats should be taken serious also in case of missing functional fertility impairment in rats. This statement is based on the by far higher sperm reserve of rats compared to human males. Thus, fertility studies in rats should be suspected to be of low sensitivity to indicate fertility impairment in human males. Considering the current picture of the database the proposal of non-classification is not plausible. Some concern on fertility impairment remain and thus a proposal on classification as Repro Cat. 2 with hazard statement H361f appears to be indicated. A discussion on additional classification for this endpoint would be desirable. Developmental toxicity -	In evaluating the available data for male fertility, we have considered the fertility study in male rabbits and effects observed in the male reproductive organs in the 2 year carcinogenicity study in rats in a weight of evidence approach. As discussed above, the evaluation of effects seen in testes, epididymis and seminal vesicles in the treated groups observed at 24 months in the carcinogenicity study is complicated by the increase in Leydig cell tumours from the mid dose group, the natural aging process of the rats and thus the less than desirable suitability of this study population to assess an effect on fertility, and the limited reporting of effects at 12 months, which would be the optimum study population. Therefore, we feel that the negative rabbit fertility study, taken with the limitations in the data from the carcinogenicity study support a proposal for no classification for male fertility.	
2009/10/14	Sweden / Swedish Chemicals Agency	Since it was provisionally agreed by TCC&L to classify for reproductive toxicity with R62, IRL has withdrawn this proposal based on arguments that the testicular toxicity observed in the 2-year rat study could be secondary to the	In November 2005, TC C&L provisionally agreed to classify TDCP as R62. However, during the follow up period to that meeting the Irish CA received additional data from the 2 year carcinogenicity study (an appendix to the	*Taking into account these comments and those from Germany the available information has been assessed. The comparison of the relevant TDCP data with the classification criteria leads RAC to the conclusion that there is*

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		formation of Leydig cell tumours or caused by the normal aging process. However, based on the Annex VI report, there seems to be little, if any, support for these hypothesis. Thus, in the repeated dose toxicity section a LOAEL of 5 mg/kg/day is reported for the testicular toxicity based on the observations of testicular toxicity in the low dose animals. As the carcinogenicity section reports NO testicular tumours in the low dose animals, it is more likely that testicular toxicity preceeds tumour formation than the other way around. It is furthermore speculated that the seminal	study report containing summary pathology results) from Industry which had previously not been made available. As a result, the Irish CA circulated a revised classification proposal of no classification for fertility. However, the revised proposal for TDCP was not discussed at another TC C&L meeting (due to ongoing studies on TCPP and V6 which were being discussed alongside TDCP). As discussed in the comment above, the Irish CA believes that the clearly negative rabbit fertility study, in combination with the lack of data at 12 months in the 2 year carcinogenicity study, in addition to the limitations of the data from the 24 month observation in that study, support a proposal of no classification for this endpoint. We agree that the incidence of Leydig cell tumours in the low dose animals is comparable to that of the control animals at both 12 and 24 months, although as noted above, the incidence at 24 months in the control animals is outside the historical control range for this tumour type. However, as discussed in the comment above, due to the limitations in the reporting of data from the 12 month	*insufficient evidence for classification of TDCP as a male reproductive toxicant.*

[2] BAUA 2006: European Union Risk Assessment Report. Tris(2-chloroethyl) phosphate, TCEP. Bundesanstalt für Arbeitsschutz und Arbeitsmedizin. Final approved version, July 2009. Available at: http://ecb.jrc.ec.europa.eu/documents/Existing-Chemicals/RISK_ASSESSMENT/REPORT/tcepreport068.pdf

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		vesicle toxicity (i.e., decreased secretory products in the seminal vesicles and athrophy of the seminal vesicles) is caused by a neoplastic process occurring in the Leydig cells, but no plausible explanation for this potential interaction between the organs are provided.	assessment, it is not possible to evaluate whether there is an association with Leydig cell tumours at this time point and whether the testicular toxicity observed at 24 months precedes tumour development. At 24 months, we agree that there appears to be effects in the seminal vesicles at all dose groups, which does not match the increase in Leydig cell tumours seen only in the mid and high dose animals. However, as discussed above, not all animals in the low and mid dose groups were evaluated for seminal vesicle effects and therefore it is possible that the incidence reported is not representative of all animals in these groups.	
		Regarding the aging process, it can of course always influence toxicity. However, with regard to atrophy of the seminal vesicles this effect is observed in 30% of the low dose animals after 24 months, which could be compared to an incidence of 0% in the controls. Aging could hardly explain this big difference. Furthermore, testicular toxicity is indicated already at 12 months by single observations in high dose animals of epididymal oligospermia and decreased secretory products in the seminal vesicles.	As discussed above, we acknowledge that there is a higher incidence of some effects in male reproductive organs in the treated groups at 24 months when compared with controls, indicating that some effects may not be due to aging process alone. However, the lack of data from the 12 month observation, particularly in the low and mid dose animals, makes evaluating the significance of a single observation of oligospermia and decreased secretory product in seminal vesicles in the high dose group difficult.	
		Finally, the testicular toxicity exerted by the analog TCEP is in our view supporting the testicular toxicity observed	There are some differences in the toxicity profile of TDCP when compared with TCEP and TCPP. In 2 year	

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		in rats by TDCP, even though the other analog TCPP is not a testicular toxicant.	carcinogenicity studies with rats and mice, TCEP showed no evidence of inducing Leydig cell or any other tumours in the male reproductive organs (BAUA, 2009)[2]. In a cross over mating trial with mice with TCEP there was evidence of an effect on sperm at the high dose of 700 mg/kg but not at the lower doses of 175 & 300 mg /kg. In a rat study, the only effect was higher sperm count at the high dose and slightly decreased sperm motility at the high dose of 175 mg/kg (77% versus 89% in the control). As discussed in section 6.9.4, in a 2-generation reproductive toxicity study with TCPP, there was no effect on male reproductive organs or fertility parameters. Given the lack of consistent effects on male fertility seen for TCEP and TCPP, a direct comparison to either substance is not considered appropriate.	
		In conclusion, we see no reason for changing the previously agreed classification with R62.	As discussed previously, the Irish CA believes that the clearly negative rabbit fertility study, in combination with the lack of data at 12 months in the carcinogenicity study, in addition to the limitations of the data from the 24 month observation in the carcinogenicity study, lead us to propose no classification for male fertility. This is in line with our amended classification proposal which was circulated to the TC C&L following the provisional agreement of this group to classify TDCP as R62.	