Committee for Risk Assessment (RAC)

Opinion

on setting Specific Concentration Limits (SCLs) for Phenol, dodecyl-, branched; Tetrapropenylphenol (TPP) as proposed by Chevron Oronite SAS

ECHA/RAC/A77-O-0000001412-86-49/F

Adopted

5 December 2014

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OPINION OF THE COMMITTEE FOR RISK ASSESSMENT

ON CHEVRON ORONITE'S CLH PROPOSAL FOR SETTING A SPECIFIC CONCENTRATION LIMITS (SCL) FOR TETRAPROPENYLPHENOL (TPP)

Pursuant to Article 77(3)(c) of Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (the REACH Regulation), the Committee for Risk Assessment (RAC) has adopted an opinion (see Annex 1) regarding Chevron Oronite's CLH proposal for setting a Specific Concentration Limits (SCL) for toxicity to reproduction of tetrapropenylphenol (TPP).

I PROCESS FOR ADOPTION OF THE OPINION

Following a request from the European Commission, in the mandate attached as Annex 2, the Executive Director of ECHA requested the Committee to review theChevron Oronite's CLH proposal for setting Specific Concentration Limits.

Rapporteur, appointed by RAC: **Anne-Lee Gustafson**

The RAC opinion was adopted on 5 December 2014. It complements the RAC opinion of 5 December 2013 on harmonised classification and labelling of tetrapropenylphenol (TPP).

The RAC opinion was adopted by consensus.

II OPINION OF RAC

With regard to the setting a Specific Concentration Limit, as requested in the above mandate, RAC assessed :

- the scientific validity of the method proposed by Chevron Oronite SAS for setting a Specific Concentration Limit,
- the suitability for this purpose of the studies brought forward by Chevron Oronite SAS with a view to Article 10(1) of the CLP Regulation and
- the compatibility of their proposal with current ECHA guidance on the topic of setting SCLs vs the Generic Concentration Limit (GCL) for reproductive toxicity.

The mandate did not request RAC to reconsider the classification of TPP as Repro. 1B and therefore this was not discussed by the Committee.

Summary: Having examined the scientific validity of the method proposed by Chevron Oronite SAS for setting a Specific Concentration Limit, the suitability for this purpose of the studies submitted by Chevron Oronite SAS on TPP mixtures in view of Article 10(1) of the CLP Regulation and the compatibility of their proposal

with current ECHA guidance on the topic of setting SCL vs the Generic Concentration Limit (GCL) for reproductive toxicity, **the Committee confirms its conclusion regarding the application of the GCL of 0.3% for toxicity to reproduction (category 1B) for tetrapropenylphenol (TPP)**.

III BACKGROUND

Two proposals for harmonised classification and labelling of tetrapropenylphenol (TPP) for reproductive toxicity were submitted to ECHA in 2012 . One CLH report was submitted by the SI Group proposing that TPP be classified in category 2 for reproductive toxicity, with no proposal for an SCL, while another CLH report from Chevron Oronite SAS proposed that TPP be classified as Repr. 1B with an SCL of 1.5%.

In December 2013 the Committee assessed both CLH proposals and adopted opinions recommending that TPP be classified as Repr. 1B, H360F without an SCL; in which case the GCL of 0.3% would therefore apply.

Chevron Oronite SAS accepted the proposed classification, but objected to the fact that no SCL was set and that the GCL would apply. The Commission postponed the inclusion of TPP (toxicity to reproduction) to Annex VI of the CLP Regulation and asked the ECHA Executive Director to mandate the Committee through an Article 77(3)(c) request to review the Chevron Oronite's CLH proposal for setting Specific Concentration Limits for reproductive toxicity.

a) Regulatory setting

The CLP Regulation (EC No 1272/2008) and the CLP guidance (Guidance on the application of the CLP criteria (Version 4)) provide instructions and guidance on how to calculate the SCL as follows:

i) **Article 10(1) of the CLP Regulation states:** "*Specific concentration limits and generic concentration limits are limits assigned to a substance indicating a threshold at or above which the presence of that substance in another substance or in a mixture as an identified impurity, additive or individual constituent leads to the classification of the substance or mixture as hazardous.*

Specific concentration limits shall be set by the manufacturer, importer or downstream user where adequate and reliable scientific information shows that the hazard of a substance is evident when the substance is present at a level below the concentrations set for any hazard class in Part 2 of Annex I or below the generic concentration limits set for any hazard class in Parts 3, 4 and 5 of Annex I.

In exceptional circumstances specific concentration limits may be set by the manufacturer, importer or downstream user where he has adequate, reliable and conclusive scientific information that a hazard of a substance classified as hazardous is not evident at a level above the concentrations set for the relevant hazard class in Part 2 of Annex I or above the generic concentration limits set for the relevant hazard class in Parts 3, 4 and 5 of that Annex."

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ii) **Article 10 (7) of the CLP Regulation states:** "*The Agency shall provide further guidance for the application of paragraphs 1 and 2*"

iii) **Table 3.7.2 in Annex I of the CLP Regulation** specifies that the GCL for ingredients of a mixture classified as reproduction toxicants Cat. 1B that trigger classification of a mixture is ≥0.3%.

iv) Further guidance on setting an SCL for substances classified as reproductive toxicants is provided in detail in **Section 3.7.2.5 of the CLP guidance**.

The approach chosen for the CLP guidance was to set SCLs based on potency in animal studies, although it is acknowledged that human data may be used in combination with animal data to set SCLs. Three potency bands were identified - high, medium and low - the first one further divided into subcategories. The approach taken was similar to the approach for setting SCLs for carcinogenicity. It should be noted that the scientific starting point for the work on establishing a standardised method for the determination of SCLs was an analysis of two databases that were created for this specific purpose. The databases contained a large number of substances classified in Annex VI to CLP as toxic to reproduction. Based on the compiled data, choices were made for the most appropriate parameter for setting the boundaries for the potency groups. Annex VI of the CLP guidance describes the process and considerations and provides the rationale. A more thorough description of the analyses performed on the databases has been published in the open literature (Muller *et al.*, 2012). The work was started by the EU working group of the Technical Committee for Classification and Labelling (TC C&L), continued under a REACH Implementation Project (RIP) and was subsequently finalised under the auspices of ECHA.

In brief, the method for setting an SCL can be described as follows:

A. The ED_{10} for effects that warrant classification was selected as the most appropriate parameter for estimating potency, since this value (in contrast to NOAEL and LOAEL) is independent of dose spacing during animal testing and takes incidence/magnitude into account. The ED_{10} was defined as the dose level which induces reproductive effects in 10% more animals than in the control group or an increase of 10% in the magnitude of the effect compared to the control group.

B. Based on ED_{10} values, the substance is then placed in a preliminary potency group. The boundaries of the potency groups were determined based on the result of analysis of potency distribution of the substances within the databases created for the SCL work (see history above). They were set in line with the provisions outlined in Article 10(1) of the CLP Regulation where it is stated that SCLs higher than GCL should be set only in "*exceptional circumstances*". Most substances were foreseen to fall into the medium potency group – which is linked to the GCL. Only substances with a very high potency should fall in the high potency group. Based on these

assumptions and the data analysis, boundaries were set such that 70-80% of the analysed substances fell into the medium potency group and ~5% and 15% in the low and high potency groups, respectively (CLP guidance VI.5.1.1.3).

C. Modifying factors (type and severity of effects, data availability, dose-response relationship, human relevance for mode or mechanism of action, toxicokinetics (e.g. the difference between humans and test species and differences between pregnant and non-pregnant animals, as well as bioaccumulation) are used to account for case-specific data situations which indicate that the potency group for a substance as obtained by the preliminary assessment, should be changed. This is particularly relevant when the preliminary potency estimate is close to the boundary between two groups.

D. Based on the final potency group an SCL is assigned according to Table 3.7.2-e of the CLP guidance

b) Summary of the approach taken by Chevron Oronite SAS to establish an SCL (more details are provided in Annexes 3 and 4).

From the different studies on TPP, Chevron Oronite SAS identified decreased ovary weight/combined weight of the ovary and the ovary duct as being the most sensitive and consistent effect on the reproductive system. Toxicological data for TPP were subsequently evaluated by Chevron Oronite SAS to identify a concentration limit for TPP that was not associated with reproductive effects in the species used for testing. The proposed SCL value (1.5%) was based on the highest No-Adverse-Effect-Level (NOAEL) for ovary weight derived from reproductive toxicity studies with TPP (Knapp *et al.*; 2006; Edwards *et al.*; 2012). The actual SCL value (as a percentage) was derived using the formula ($NOAEL_{highest}$ /1000) * 100. The denominator, 1000 mg/kg bw, represents the limit dose given in the OECD guideline TG 416. Chevron Oronite SAS justified the use of a limit dose by referring to OECD 416 test guideline which indicates that 1000 mg/kg bw/day can be the maximum dosage tested "*except when human exposure indicates the need for a higher oral dose level to be used. For other types of administration, such as inhalation or dermal application, the physical chemical properties of the test substance, such as solubility, often may dictate the maximum attainable concentration*." Due to the physical chemical properties of TPP (high viscosity, very low volatility) and its use (manufacturing intermediate for additive packages and engine oils), Chevron Oronite SAS argues that they have no reason to believe that human exposure would warrant a higher potential test dose than 1000 mg/kg bw/day. They provide a large amount of exposure data supporting the argument that during normal use, exposure to TPP is indeed well below 1000 mg/kg bw/day for the TPP containing substances marketed by Chevron Oronite SAS. RAC notes that this data is of limited use for classification, and consequently for setting an SCL, as classification is based on the intrinsic properties of the substance and thus use is not taken into account in classification (see section 1.2 of the CLP guidance for more details).

Although Chevron Oronite SAS based their SCL calculations on NOAELs, they also provided ED_{10} calculations for the observed effects on ovary weights (a summary of the data provided by Chevron Oronite SAS is presented in the table below). The company noted (page 19 of Annex 4) that *"Use of the LED_{10}, the lower confidence interval value for the ED_{10}, derived a slightly higher value, 1.86% (18.6 mg TTP/kg/day), than the SCL determined by the NOAEL method"* but argued that "*The existence of multiple sets of empirical data that ≤ 15 mg/kg/day does not result in TTP –derived reproductive toxicity is sufficient evidence to establish the SCL*".

Study	**ED_{10}** (mg/kg bw/day) by linear extrapo-lation[1]	**NOAEL** (mg/kg bw/day)	**ED_{10}** (by Bench Mark Dose software)[2]	**Reference**
Oral (gavage) 1-generation reproductive toxicity study in rat (OECD 415, dose levels: 0, 5, 25, 125 mg/kg bw/day)	20.5	5	18.6	Knapp *et. al.* 2006
Oral (dietary) 2-generation reproductive toxicity study in rat (OECD 416, dose levels: 0, 1.5, 15, 75 mg/kg bw/day)	27.2 (F_0)	15	20.3	Edwards *et. al.* 2012
	28.5 (F_1)	15	40.8	
Oral (dietary) 90 day repeated toxicity study in rat (OECD 408, dose levels: 0, 50, 100, 150 & 200 mg/kg bw/day)	No data provided	50	53.8	Haas *et. al.* 2012

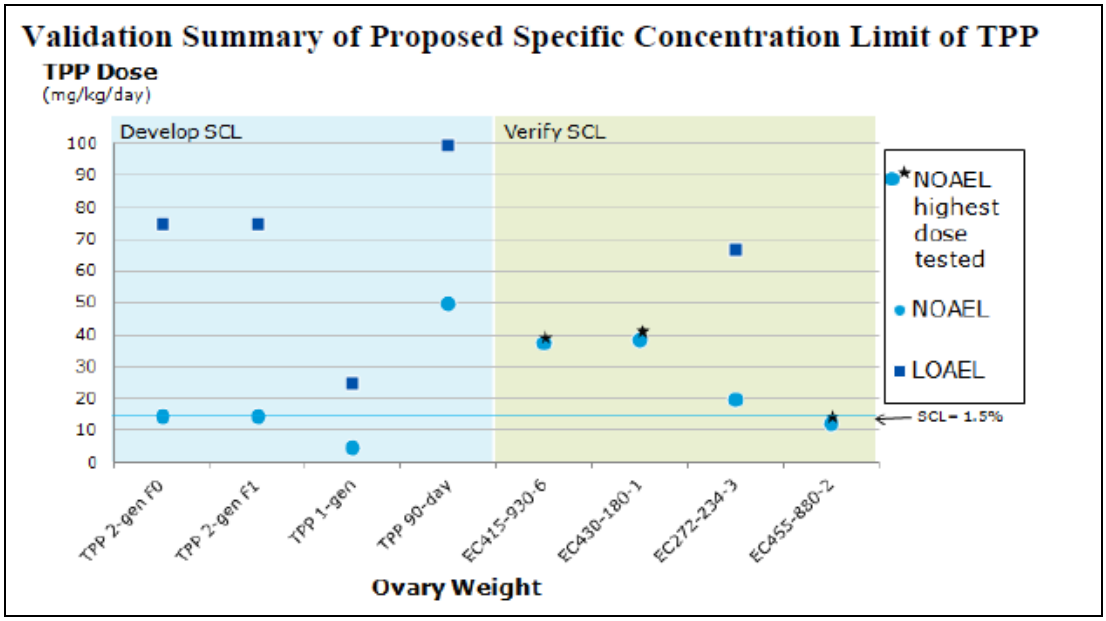
1) This data was provided during public consultation

2) It is noted that the methodology used by Chevron Oronite SAS to calculate the ED_{10} value (i.e. using the LED_{10}) was questioned during PC by an MSCA who argued that the BMR of one standard deviation below the control mean value was not considered to represent a 10% effect level above the background (see Annex 3 for more details). Furthermore, the lowest ED_{10} value (18.6 mg/kg/day; Knapp *et al.* 2006) calculated by the BMD methodology only differs marginally from the one calculated by the linear extrapolation methodology (20.5 mg/kg bw/d). The latter ED_{10} value is also in agreement with the ED_{10} value provided in the RAC opinion for this endpoint. It can be concluded that all ED_{10} values are reasonably similar for the different studies irrespective of the calculation method.

c) *Summary of the approach taken by Chevron Oronite SAS to verify the SCL*

Chevron Oronite SAS attempted to verify the SCLs against the pre-existing test data from four reproductive toxicity studies conducted with four different TPP-containing UVCBs. The concentration of TPP in these UVCBs ranged from 2.5 wt% to 26 wt% TPP, with tested dose levels of 1.25 mg TPP/kg bw/day to 67 mg TPP/kg bw/day (see Annex 2 for detailed information on the composition of these UVCBs as well as details of the result from the studies performed).

The figure below, which is reproduced from Annex 3, was used by Chevron Oronite SAS to illustrate the distribution of the NOAELs and LOAELs for effects on ovary weight for TPP itself as well as for the TPP containing UVCBs. In the RCOM document (page 19 of Annex 4) Chevron Oronite SAS concluded that "*There were no effects upon TPP-responsive reproductive parameters in these studies at dosage levels below 15 mg/kg/day".*



Chevron Oronite SAS stated in the RCOM (Annex 4, page 26) that:

"*The guidance provided by ECHA for the application of the CLP criteria (version 3.0; November 2012) specifically cites (page 330) that '…specific concentration limits may be set by the manufacturer, importer or downstream user where he has adequate, reliable and conclusive scientific information that a hazard of a substance classified as hazardous is not evident at a level above the concentrations set for the relevant hazard class in part 2 of Annex I or above the generic concentration limits set for the relevant hazard class…' For TPP, we believe that we meet the criteria of:*

'adequate' – two reproduction studies conducted with TPP, four reproduction studies conducted with substances that contain TPP at 1.25 wt.% to 26 wt.%

'reliable' – all studies were conducted to meet or exceed OECD test guidelines and adhered to Good Laboratory Standards

'conclusive' – the results of four reproduction studies conducted to OECD test guideline standards validated that none of the reproductive effects associated with TPP were observed at exposures of 15 mg TPP/kg/day or lower. Additional animal testing is unjustified. Therefore, in accordance with the published guidance, we have self-classified substances that contain TPP at greater than 1.5 wt.%."

In the opinion of Chevron Oronite SAS, validation with existing data is preferable to selection of a default method, which they claim lacks a clear scientific basis

The results from the reproductive toxicity studies using the TPP-containing UCVBs were summarised in the CLH report (page 121 of Annex 3) by Chevron Oronite SAS as follows:

i. EC 415-930-6 was evaluated in a rat oral (gavage) two-generation reproduction study (Wood et al., 2002). At the test substance doses of 0, 50, 250 and 1000 mg/kg/day, the dose levels of TPP were 0, 1.9, 9.5, and 38 mg/kg/day. The parental NOAEL was 50 mg/kg/day (1.9 mg TPP/kg/day). The reproductive NOAEL was 250 mg/kg/day (9.5 mg TPP/kg/day) based upon reductions to pregnancy index and litter size at 1000 mg/kg/day (38 mg TPP/kg/day). Ovary weight was not reduced in

females of either generation, suggesting that the TPP-derived substance was of lesser potency for this effect.

ii. EC 430-180-1 was evaluated in a rat oral (gavage) two-generation reproduction study (Wood et al., 2003). At test substance doses of 0, 5, 30, or 150 mg/kg/day, the dose levels of TPP were 0, 1.3, 7.8, and 39 mg/kg/day. Ovary weight was not reduced in females of either generation. At 150 mg/kg/day (39 mg TPP/kg/day) female offspring achieved vaginal opening at a younger mean age (31.6 days versus 34.2 days) and lower average body weight in comparison to the concurrent control females. The NOAEL for vaginal patency was 30 mg/kg/day (7.8 mg TPP/kg/day).

iii. EC 272-234-3 was evaluated in a rat oral (gavage) two-generation reproduction study (Nemec et al., 1995). At test substance doses of 0, 50, 300, and 1000 mg/kg/day, the dose levels of TPP were 0, 3.4, 20.1, and 67 mg TPP/kg/day. Fertility and live litter size were reduced at 1000 mg/kg/day (67 mg TPP/kg/day); satellite groups that were cross-mated during the second generation (exposed males x unexposed females; unexposed males x exposed females) identified that these effects resulted from treatment of the female. Ovary weight was reduced at 1000 mg/kg/day (67 mg TPP/kg/day); the NOAEL for this parameter was 300 mg/kg/day (20.1 mg TPP/kg/day).

iv. EC 455-880-2 was evaluated in a rat oral (gavage) one-generation reproduction study (Knapp et al., 2008). At test substance doses of 0, 50, 170, and 500 mg/kg/day, the dose levels of TPP were 0, 1.25, 4.25, and 12.5 mg TPP/kg/day.

IV. SCIENTIFIC GROUNDS FOR THE OPINION

a) *Scientific validity of the method used by Chevron Oronite SAS to set the SCL.*

The method used by Chevron Oronite SAS is identical to a method that was historically used by the TC C&L for setting SCLs for a few substances (see Annex 5).

Scientific basis of the method

The method is based on a number of assumptions

1. A dose where no effect is seen in animal experiments is safe for humans (i.e.- $NOAEL_{animal}$ = $NOAEL_{humans}$). This assumption is not correct. In most cases information on a NOAEL for effects on humans will never be available and the procedure that is used in Risk Assessment processes to take into account inter-species as well as intra-species differences is to include various assessment factors that compensate for these uncertainties (see REACH guidance). Thus a DNEL derived for workers or the general population is normally much lower than the NOAEL observed in animal tests. Similarly, some of the modifying factors used for assigning the final potency group in the procedure for setting an SCL according to the CLP guidance, should be viewed as a way of taking

differences in mode/mechanism of action and differences in toxicokinetics between test species and humans into consideration.

2. That a NOAEL is a good descriptor for an effect level. This assumption is not correct. According to Article 10(1) of the CLP Regulation: *"Specific concentration limits and generic concentration limits are limits assigned to a substance indicating a threshold at or above which the presence of that substance […] leads to the classification […."*. It thus seems more logical to use an LOAEL instead of a NOAEL as a descriptor for such a level. In addition, since LOAELs (as well as NOAELs) will be dependent on the dose levels/dose spacing used in the experiments, there is greater objectivity in using an ED_{10} (which is independent of dose levels chosen in a particular experiment) as a standardised descriptor of an effect level.

3. The use of a limit dose of 1000 mg/kg bw/day is based on the assumption that 1000 mg/kg bw/day will always be the highest assumed human exposure for TPP. From a regulatory perspective, it is noted by RAC, that the CLP Regulation (sections 3.7.2.5.6. – 3.7.2.5.9) does not include within the criteria a specific dose as a limit dose but that some guidelines for test methods specify a limit dose, while others qualify the limit dose with a statement that higher doses may be necessary if anticipated human exposure is sufficiently high that an adequate margin of exposure is not achieved. RAC therefore concludes that the concept of limit dose is only useful in the context of dose selection/data interpretation of guideline studies but is less relevant for classification (and consequently not for SCL determination).

   RAC also notes that the CLP Regulation (section 3.7.2.5.7) states "*Also, due to species differences in toxicokinetics, establishing a specific limit dose may not be adequate for situations where humans are more sensitive than the animal model"*. No information has been provided by Chevron Oronite SAS which indicates that humans are less sensitive towards the effects observed or which indicates that due to toxicokinetic (TK) differences the rat should not be considered as a valid model. RAC concludes that from a strictly scientific perspective (and assuming that the use of 1000 mg/kg bw had been acceptable), inclusion of assessment factors to account for these uncertainties would be needed. Thus also from this perspective the use of the formula [$NOAEL_{animal}$ / 1000] x 100 without assessment factors does not seem to provide a sufficient level of protection.

RAC notes that the approach taken in the CLP Guidance on how to calculate an SCL for effects on reproduction is in line with how an SCL is determined for another hazard class (carcinogenicity). Thus, from a scientific as well as a regulatory viewpoint it would be inconsistent to apply different methods for these endpoints.

In conclusion, it is argued by the company that the method which they propose would be scientifically more adequate than the method recommended in the CLP guidance. Based on the argumentation provided above, RAC does

not - from a scientific point of view - agree with this conclusion. In addition, Chevron Oronite SAS does not provide any reference to other CLH reports or to reports from other regulatory bodies outside Europe that deal with SCLs in the context of the GHS that would support their argumentation. On the contrary, it is noted that in 2014, RAC has revisited several of the entries in Annex VI to the CLP Regulation where the method used by Chevron Oronite SAS to set SCLs have been used historically. In these cases, the Committee agreed with the DSs proposals that the higher SCLs set by this method should be removed (for DIBP, DMAC and NMP[1]). For DOT[2] and DOA[3], which are new borate entries, no SCL was set, in contrast to earlier borates in Annex VI, as RAC did not find it justified.

Regulatory aspects

The method used by Chevron Oronite SAS poses several issues from a regulatory viewpoint.

The CLP Regulation (Art. 10(1) states that: "*In exceptional circumstances specific concentration limits may be set by the manufacturer, importer or downstream user where he has adequate, reliable and conclusive scientific information that a hazard of a substance classified as hazardous is not evident at a level above the concentrations set for the relevant hazard class in Part 2 of Annex I or above the generic concentration limits set for the relevant hazard class in Parts 3, 4 and 5 of that Annex*."

This method proposes SCLs which are higher than the GCL for about 75% (Muller *et al.*, 2012) of all substances, which does not seem to be compatible with the intention of the CLP Regulation.

RAC also notes that it's previous opinion on TPP[4] concluded that this substance should be classified in Category 1B for reproductive toxicity and that there were no findings in the data set to suggest either especially high or low potency. In this respect, the identified ED_{10} values for TPP (range: 4.3 – 33.75 mg/kg bw/day) were within the boundary ($4 \geq ED_{10} \leq 400$ mg/kg bw/day) for the medium potency group defined in the CLP guidance and the evaluation of the modifying factors gave no reason to suggest that TPP belonged to another potency group. Based on this, RAC concludes that the

[1] Opinion No. CLH-O-0000004066-78-03/F of 6 June 2014; http://echa.europa.eu/opinions-of-the-committee-for-risk-assessment-on-proposals-for-harmonised-classification-and-labelling/-/substance/84/search/+/del/75/col/OPINIONDATERAC/type/desc/pre/1/view

[2] Opinion No. CLH-O-0000003655-70-03/F of 14 March 2014; http://echa.europa.eu/opinions-of-the-committee-for-risk-assessment-on-proposals-for-harmonised-classification-and-labelling/-/substance/6206/search/+/del/75/col/OPINIONDATERAC/type/desc/pre/1/view

[3] Opinion No. CLH-O-0000003654-72-03/F of 14 March 2014; http://echa.europa.eu/opinions-of-the-committee-for-risk-assessment-on-proposals-for-harmonised-classification-and-labelling/-/substance/6205/search/+/del/75/col/OPINIONDATERAC/type/desc/pre/1/view

[4] Opinion No. CLH-O-0000003405-79-03/F of 5 December 2013; http://echa.europa.eu/opinions-of-the-committee-for-risk-assessment-on-proposals-for-harmonised-classification-and-labelling/-/substance/5730/search/+/term

dataset on TTP in itself is not 'exceptional' and does not provide support for deviating from the method recommended in the CLP guidance.

b) *Suitability for the purpose of setting SCLs of studies provided by Chevron Oronite SAS in relation to Article 10(1) of the CLP Regulation*

As discussed in the RAC opinion on TPP, the studies on TPP itself are suitable (data were from OECD guideline studies of high quality) for setting SCLs. The studies on the various UVCBs containing TPP are also OECD TG studies of high quality. Taken together, RAC notes that the results from these studies do not contradict the Repr. 1B classification for TPP. However, in addition to TPP these UVCBs contain other components (see Annex 3) and from the data provided by Chevron Oronite SAS it is not possible to conclude whether the observed effects are solely due to TPP. In fact there are occasions where effects are noted as not being observed for TPP (e.g. delayed sexual maturation of males). In addition, it has not been proven that all UVCBs can cause effects on ovary weight (the key endpoint used by Chevron Oronite SAS in their verification of the SCL for TPP).

Thus RAC concludes that the data provided on the UVCBs are reliable and conclusive for classification of the TPP-containing UVCBs. However the data provided on the TPP-containing UVCBs are not adequate, reliable, nor conclusive for classification of TPP itself and are thus not suitable for setting an SCL for TPP and consequently the data are also not suitable for verifying the proposed SCL for TPP.

RAC evaluation of the data on TPP containing UVCBs

RAC notes that no reductions in ovary weight were recorded for 3 out of 4 of the UVCBs used (EC 430-180-1, EC 455-880-2, EC 415-930-6). RAC acknowledges that one possible reason for this could be that the dose levels used were too low, as only minor or no effects on female body weight were recorded in these studies. However, as documented in the original CLH report, these UVCBs also contain other components of unknown toxicity and it has not been conclusively documented to what extent these components influence the toxicity observed for these UVCBs. RAC also notes that Chevron Oronite SAS comments on the lack of effect on ovary weight for the UVCB EC 415-930-6 at 38 mg/kg bw/day of TPP with the comment "*Ovary weight was not reduced in females of either generation, suggesting that the TPP-derived substance was of lesser potency for this effect."* (page 120 of Annex 3). RAC concludes that this statement most likely is a reflection of the fact that based on data from TPP itself (Knapp *et al.,* 2006; $LOAEL_{ovary\ weight}$ = 25 mg/kg bw/day) a reduction in ovary weight was expected to also be observed at the highest TPP dose (38 mg/kg bw/day) used in this study with EC 415-930-6.

RAC notes that no other data using higher dose levels (for example from repeated dose toxicity studies) have been provided by Chevron Oronite SAS on these 3 UVCBs. Without knowing if these UVCBs indeed can cause effects on ovary weight, albeit at higher doses, it is not possible or appropriate to use the reported $NOAEL_{ovary\ weight}$ from these studies in a weight of evidence (WoE)

approach to verify an SCL for TPP, especially since this SCL was based on effects on ovary weights.

RAC also notes that the graphical presentation of the data that Chevron Oronite SAS provided for their validation summary of the proposed specific concentration limit of TPP (see page 6 of this document) refers to effects on ovary weight. Chevron Oronite SAS, however, worded its conclusion to state that the results from the studies are conclusive since *"the results of four reproduction studies conducted to OECD test guideline standards validated that none of the reproductive effects associated with TPP were observed at exposures of 15 mg TPP/kg/day or lower."* Although this statement is compatible with the data provided, the data does not exclude the possibility of effect at lower exposures. When summarising the results for e.g. EC 430-180-1, Chevron Oronite SAS stated that "*The NOAEL for vaginal patency was 30 mg/kg/day (7.8 mg TPP/kg/day)*" i.e. a NOAEL below 15 mg TPP/kg bw/day. The data provided indicates that the lowest actually observed level for this effect was 39 mg/kg TPP (the next dose level). RAC concludes that a closer spacing of doses would possibly give another LOAEL, which could potentially be at or below 15 mg/kg bw/day.

In addition, RAC notes that the data that are available for some of these UVCBs do indicate that these TPP-containing UVCBs can cause reproductive toxicity that is not due to TPP, i.e. it is due to the UVCB substance in itself. For example, for EC 415-930-6, delayed sexual maturation with increased body weight was recorded for males at 9.5 mg/kg bw/day of TPP. Chevron Oronite SAS acknowledge that the recorded delay in male sexual maturation observed in this study is attributed to the test compound and not to the TPP content in the substance, as it conflicts with the TPP findings (page 104 of Annex 3).

c) *Compatibility of the proposal with the current CLP guidance (setting of SCLs)*

Section VI.5.1.1.4 of the CLP guidance states "*Several other options for a method for determining SCLs were discussed including a method that was used by the TC C&L in a limited number of cases in the past. This method is based on the limit dose of 1000 mg/kg bw/day, as described in the test guideline OECD 414 and 416.*

The concentration limit expressed as a % in mixtures is derived by dividing the NOAEL by the limit dose followed by multiplication by 100 (see ECBI/47/02 Add.7). This method would result in an individual SCL for each substance. This would indicate a precision that cannot be expected from standard reproduction studies. Also this would result in an SCL for most substances and in a GCL for only some substances. Therefore, this method was not considered. […]".

RAC concludes that the method used is not only the one not recommended, but it is actually discouraged by the CLP guidance.

References

Edwards, TL. *et al*. (2012). A dietary two-generation productive toxicity study of tetrapropenyl phenol in rats. WIL Research Laboratories, LLC, Study No. WIL-186053, Conducted for the American Chemistry Council.

Haas, MC. *et al*. (2012). A 90-day dietary dose range-finding toxicity study of tetrapropenyl phenol in rat. WIL Research Laboratories, LLC, Study No. WIL-186054; Conducted for the American Chemistry Council.

Knapp, JF. *et al*. (2006). An Oral (Gavage) One-Generation Reproductive Toxicity Study of Tetrapropenyl Phenol in Rats. WIL Research Laboratories, LLC, Study No. WIL-186033. Conducted for the American Chemistry Council Petroleum Additives Panel Health Environmental and Regulatory Task Group.

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ANNEXES

Annex 1	RAC Opinion of 5 December 2013 proposing harmonised classification and labelling at EU level of Phenol, dodecyl-, branched [1]; Phenol, 2-dodecyl-, branched; Phenol, 3-dodecyl-, branched; Phenol, 4-dodecyl-, branched; Phenol, (tetrapropenyl) derivatives [2].
Annex 2	Request from the Executive Director of ECHA to RAC – 'the mandate'.
Annex 3	Background Document to RAC Opinion of 5 December 2013 proposing harmonised classification and labelling at EU level of Phenol, dodecyl-, branched [1]; Phenol, 2-dodecyl-, branched; Phenol, 3-dodecyl-, branched; Phenol, 4-dodecyl-, branched; Phenol, (tetrapropenyl) derivatives [2].
Annex 4	RCOM document to RAC Opinion of 5 December 2013 proposing harmonised classification and labelling at EU level of Phenol, dodecyl-, branched [1]; Phenol, 2-dodecyl-, branched; Phenol, 3-dodecyl-,

branched; Phenol, 4-dodecyl-, branched; Phenol, (tetrapropenyl) derivatives [2]

Annex 5 Extract from Annex VI of CLP of substances where SCL was set by the TC C&L