

Committee for Risk Assessment
RAC

Annex 2

Response to comments document (RCOM)
to the Opinion 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]

EC number: 310-154-3 [1]
CAS numbers: 121158-58-5 [1], 74499-35-7 [2]

CLH-O-0000003405-79-03/A2

Adopted
5 December 2013

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON PHENOL, DODECYL-, BRANCHED [TETRAPROPENYLPHENOL (TPP)]

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COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in this table as submitted by the webform. Please note that some attachments received may have been copied in the table below. The attachments received have been provided in full to the dossier submitter and RAC.

ECHA accepts no responsibility or liability for the content of this table.

Substance name: Phenol, dodecyl-, branched [Tetrapropenylphenol (TPP)]

EC number: 310-154-3

CAS number: 121158-58-5

Dossier submitter: Industry (Chevron Oronite SAS)

GENERAL COMMENTS

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|----------------|--------------|-------------------------|----------------|
| 19.04.2013 | United Kingdom | | Company-Downstream user | 1 |
| Comment received | | | | |
| As per the first CLH dossier submitted for Phenol, dodecyl-, branched, my Company supports the classification of phenol, dodecyl-, branched as Repr. Cat. 2. RAC needs to ensure consistency with previous RAC opinions on the classification for reproductive toxicity and Category 2 for reprotoxicity would appear to be consistent. We do have concerns over the criteria for applying these reproductive classifications being not sufficiently well defined and potentially allow different conclusions to be drawn. Additional guidance for this end point would be welcome. | | | | |
| Dossier Submitter's Response | | | | |
| We agree with the philosophy of Comment 1 in support of consistent application of reproductive toxicity classification criteria by RAC. | | | | |
| RAC's response | | | | |
| The option of classification of TPP as Repr. 2 was considered by RAC; however, classification as Repr. 1B was considered justified based on the information provided to RAC. The rationale and justification for the classification as Repr. 1B is contained in the opinion document. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---------|--------------|----------------------|----------------|
| 15.04.2013 | Denmark | | MemberState | 2 |
| Comment received | | | | |
| For setting the SCL: As the REACH Review according Art. 138 (7) for endocrine disrupting substances including the possibility to determine threshold values for these substances is currently up for discussion , the time for setting specific concentration limit for a substance that might very well be defined as a endocrine disruption substances could be very inappropriate. | | | | |
| Dossier Submitter's Response | | | | |
| As stated in Comment 2, further regulatory guidance related to interpretation of hazards and risks associated with endocrine active substances may be forthcoming. Our evaluation of the toxicity test results and proposal for an SCL are based upon classification criteria for a reproductive toxicant and the identification of adverse reproductive effects in alignment with current ECHA guidance. | | | | |
| RAC's response | | | | |

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The calculations of the concentration limits in the RAC opinion are based on based on the new Guidance on the application of the CLP criteria (Version 4.0 – November 2013, section 3.7.2.5. Setting of specific concentration limits). For medium potency substances, such as TPP, the GCL should be used, namely 0.3 % for substances classified as Repr. 1B according to the CLP Regulation.

| Date | Country | Organisation | Type of Organisation | Comment number |
|------------|-------------|--------------|----------------------|----------------|
| 09.04.2013 | Netherlands | RIVM | National Authority | 3 |

Comment received

p.52-57 Please provide the detailed results in the tables by generation (two generations are now taken together) so statements in the text can be better verified. Please also provide the data on pup weights (described on p. 53) in the tables.
P. 85-113: For clarity reasons please provide tables of the results, for a better overview than the textual lists of results.

Dossier Submitter's Response

Regarding the text of Page 85 – 113: For optimal transparency, we are currently pursuing the option to make the toxicology report available to commenters through ECHA. This will enable commenters to review all of the methods, data, and interpretative text by the study director.

Regarding the tables, Page 52 – 57: For benefit of the Commenter, the table in the submission, page 54-55, is split below to separate results of the F0 and F1 females, followed by tables for the F0 and F1 males. Pup weight has been added to the female tables.

Key Findings: Effects on Female Reproductive Parameters – F0 (Edwards et al., 2012)

| Parameter F0 females and offspring | Dose Level (mg/kg/day) | | | |
|---|------------------------|----------|----------|-----------------|
| | 0 | 1.5 | 15 | 75 |
| Mean Absolute Organ Weights and Microscopic Findings (incidence) | | | | |
| Mean Terminal Body Weight (g) | 325 | 323 | 321 | 286** (↓12%) |
| Mean Body Weight (g) - Initiation of Mating | 293 | 290 | 284 | 256** (↓12.6%) |
| Mean Body Weight Gain (g) – Initiation of Mating | 126 | 123 | 117 | 89** (↓29.4%) |
| Mean Ovaries Weight (g) | 0.1202 | 0.1210 | 0.1142 | 0.0846** (↓30%) |
| Ovaries – decreased presence of corpora lutea (5 or less) | 1/30 | 0/27 | 0/30 | 6/28* |
| Estrous Cycle Length (days) (Historical Control Range: 3.6 – 5.8 d) | 4.3 | 4.3 | 4.5 | 5.4** |
| Persistent Estrus (>3 consecutive days) | 1/30 | 0/30 | 0/30 | 0/30 |
| Persistent Diestrus (>4 consecutive days) | 0/30 | 0/30 | 6/30 | 12/30 |
| Number Implantation Sites (measured in F0 only) (Historical Control Range: 12.6 – 17.0) | 15.0 | 14.8 | 14.7 | 13.2* (↓12%) |
| Number Born (Historical Control Range: 13.0 – 16.6) | 14.0 | 14.1 | 14.0 | 12.5 |
| Live Litter Size (Historical Control Range: 12.6 - 16.4) | 13.8 | 13.9 | 13.7 | 12.2 |
| Pup Weight (M/F) – PND 1 | 7.5/7.0 | 7.5/7.0 | 7.3/6.9 | 7.2/6.8 |
| Pup Weight (M/F) – PND 4 | 10.4/9.8 | 10.2/9.6 | 10.0/9.6 | 9.6/9.0 |

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| | | | | |
|---------------------------|-----------|-----------|--------------|---------------|
| Pup Weight (M/F) – PND 7 | 16.5/15.7 | 16.1/15.3 | 15.1*/14.4** | 14.3**/13.5** |
| Pup Weight (M/F) – PND 14 | 30.1/29.2 | 30.1/29.1 | 28.6/27.3 | 22.9**/21.8** |
| Pup Weight (M/F) – PND 21 | 50.7/49.3 | 49.1/46.8 | 47.0/45.0* | 36.4**/34.4** |

Statistical significance: *p<0.05; **p<0.01

(Historical Control Range (2000 – 2009) provided with the report (Edwards, 2012); minimum/maximum values)

Key Findings: Effects on Female Reproductive Parameters – F1 (Edwards et al., 2012)

| Parameter F1 females and offspring | Dose Level (mg/kg/day) | | | |
|---|------------------------|-----------|-----------|-----------------|
| | 0 | 1.5 | 15 | 75 |
| Mean Absolute Organ Weights and Microscopic Findings (incidence) | | | | |
| Mean Terminal Body Weight (g) | 413 | 389 | 383 | 315** (↓24%) |
| Mean Body Weight (g) – Initiation of Mating | 319 | 313 | 309 | 279** (↓12.5%) |
| Mean Body Weight Gain (g) – Initiation of 1 st Mating | 164 | 167 | 159 | 145** (↓11.6%) |
| Mean Ovaries Weight (g) | 0.1051 | 0.0993 | 0.1027 | 0.0651** (↓38%) |
| Ovaries – decreased presence of corpora lutea (5 or less) | 6/28 | 2/28 | 3/30 | 16/26* |
| Estrous Cycle Length (days) | 4.3 | 4.2 | 4.6 | 6.5** |
| Vaginal Patency (F1 only) (days) | 32.4 | 32.2 | 32.4 | 27.4** (↓15%) |
| Persistent Estrus (>3 consecutive days) | 0/30 | 0/30 | 0/30 | 2/27 |
| Persistent Diestrus (>4 consecutive days) | 8/30 | 4/30 | 9/30 | 20/27 |
| Number Implantation Sites (measured in F0 only) | 15.0 | 14.8 | 14.7 | 13.2* (↓12%) |
| Number Born (F2/F2a) | 13.4/13.4 | 13.0/13.1 | 13.2/13.3 | 12.6/10.1* |
| Live Litter Size(F2/F2a) | 13.3/13.4 | 12.9/12.7 | 13.0/13.1 | 12.1/9.5* |
| F2: | | | | |
| Pup Weight (M/F) – PND 1 | 7.4/7.0 | 7.4/6.9 | 7.1/6.7 | 6.7*/6.3** |
| Pup Weight (M/F) – PND 4 | 10.5/9.9 | 10.8/10.2 | 10.5/9.6 | 9.8/9.1 |
| Pup Weight (M/F) – PND 7 | 16.8/15.9 | 17.4/16.3 | 16.8/15.3 | 15.4/14.2* |
| Pup Weight (M/F) – PND 14 | 33.9/32.5 | 34.9/33.7 | 33.7/31.5 | 29.0**/27.9** |
| Pup Weight (M/F) – PND 21 | 51.9/49.6 | 52.6/50.5 | 52.7/48.9 | 40.9*/39.4** |
| F2a | | | | |
| Pup Weight (M/F) – PND 1 | 7.4/7.0 | 7.4/7.0 | 7.1/6.7 | 7.1/6.8 |
| Pup Weight (M/F) – PND 4 | 10.6/10.0 | 11.0/10.3 | 10.1/9.5 | 10.2/10.1 |
| Pup Weight (M/F) – PND 7 | 16.8/15.8 | 17.4/16.3 | 15.6/14.7 | 15.3/15.2 |
| Pup Weight (M/F) – PND 14 | 33.9/32.5 | 34.9/33.2 | 31.8/30.7 | 28.4**/28.4* |
| Pup Weight (M/F) – PND 21 | 53.1/50.0 | 54.3/51.3 | 51.2/48.3 | 42.8**/42.1** |

Statistical significance: *p<0.05; **p<0.01

Key Findings: Effects on Male Reproductive Parameters – F0 (Edwards et al., 2012)

| Parameter F0 Males (F1 offspring) | Dose Level (mg/kg/day) | | | |
|--|------------------------|------|------|----------------|
| | 0 | 1.5 | 15 | 75 |
| Mean Organ Absolute Weights (unless stated) and Microscopic Findings (incidence) | | | | |
| Mean Terminal Body Weight (g) | 616 | 623 | 611 | 502** (↓18.5%) |
| Mean Testes Weight (g) Left | 1.79 | 1.69 | 1.75 | 1.62* (↓5%) |
| Mean Testes Weight (g) Right | 1.78 | 1.74 | 1.70 | 1.66 |

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| | | | | |
|--|--------|--------|--------|-----------------|
| Mean Epididymides Weight (g) Left | 0.75 | 0.72 | 0.76 | 0.63** (↓16%) |
| Mean Epididymides Weight (g) Right | 0.79 | 0.76 | 0.79 | 0.68** (↓13.9%) |
| Epididymis Sperm Concentration (x106/g) Left | 365.2 | 333.6 | 357.3 | 288.5* (↓26%) |
| Mean Cauda Epididymides Weight (g) Left | 0.3666 | 0.3339 | 0.3755 | 0.2747** (↓25%) |
| Mean Cauda Epididymides Weight (g) Right | 0.3671 | 0.3529 | 0.3686 | 0.2838** (↓23%) |
| Mean Cauda Epididymis Weight Relative to Body Weight (g/100g) Left | 0.060 | 0.054 | 0.062 | 0.055 |
| Mean Cauda Epididymis Weight Relative to Body Weight (g/100g) Right | 0.060 | 0.057 | 0.061 | 0.057 |
| Mean Cauda Epididymis Weight Relative to Brain Weight (g/100g) Left | 16.892 | 15.530 | 17.450 | 12.818** (↓24%) |
| Mean Cauda Epididymis Weight Relative to Brain Weight (g/100g) Right | 16.885 | 16.483 | 17.137 | 13.235** (↓22%) |
| Mean Prostate Weight (g) | 1.13 | 1.09 | 1.09 | 0.88** (↓22%) |
| Mean Prostate Weight Relative to Brain Weight (g/100g) | 51.959 | 50.983 | 50.633 | 41.039** (↓21%) |
| Mean Seminal Vesicle Weight (g) | 2.34 | 2.22 | 2.31 | 1.74** (↓26%) |
| Mean Seminal Vesicle Weight Relative to Body Weight (g/100g) | 0.404 | 0.359 | 0.379 | 0.346 (↓14%) |

Statistical significance: *p<0.05; **p<0.01

Key Findings: Effects on Male Reproductive Parameters – F1 (Edwards et al., 2012)

| Parameter F1 Males | Dose Level (mg/kg/day) | | | |
|--|------------------------|----------------|-----------------|-----------------|
| | 0 | 1.5 | 15 | 75 |
| Mean Organ Absolute Weights (unless stated) and Microscopic Findings (incidence) | | | | |
| Mean Terminal Body Weight (g) | 791 | 814 | 754 | 566** (↓28.4%) |
| Mean Body Weight (g) - Initiation of Mating | 543 | 545 | 536 | 449** (↓17.3%) |
| Mean Testes Weight (g) Left | 1.87 | 1.94 | 1.94 | 1.74 |
| Mean Testes Weight (g) Right | 1.93 | 1.96 | 1.88 | 1.72** (↓11%) |
| Mean Epididymides Weight (g) Left | 0.67 | 0.73 | 0.75* (↑12%) | 0.65 |
| Mean Epididymides Weight (g) Right | 0.76 | 0.80 | 0.77 | 0.68** (↓10.5%) |
| Epididymis Sperm Concentration (x106/g) Left | 310.1 | 339.4 | 350.2 | 320.5 |
| Mean Cauda Epididymides Weight (g) Left | 0.3028 | 0.3362 | 0.3391* (↑12%) | 0.2740 |
| Mean Cauda Epididymides Weight (g) Right | 0.3349 | 0.3588 | 0.3372 | 0.2879** (↓14%) |
| Mean Cauda Epididymis Weight Relative to Body Weight (g/100g) Left | 0.039 | 0.042 | 0.046** | 0.049** (↑25%) |
| Mean Cauda Epididymis Weight Relative to Body Weight (g/100g) Right | 0.043 | 0.045 | 0.045 | 0.052** (↑21%) |
| Mean Cauda Epididymis Weight Relative to Brain Weight (g/100g) Left | 13.751 | 15.663* (↑14%) | 15.825** (↑15%) | 13.116 |
| Mean Cauda Epididymis Weight Relative to Brain Weight (g/100g) Right | 15.253 | 16.714 | 15.720 | 13.815 |
| Mean Prostate Weight (g) | 1.06 | 1.07 | 1.06 | 0.92* (↓13%) |
| Mean Prostate Weight Relative to Brain Weight (g/100g) | 48.133 | 49.916 | 49.262 | 44.003 |
| Mean Seminal Vesicle Weight (g) | 2.19 | 2.26 | 2.2 | 1.81** (↓17) |
| Mean Seminal Weight Weight Relative to Body Weight (g/100g) Right | 0.28 | 0.284 | 0.296 | 0.32** (↑14%) |

Statistical significance: *p<0.05; **p<0.01

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| RAC's response |
| Thank you for your comment, the additional data were used in the RAC conclusion. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|------------|---------|--------------|----------------------|----------------|
| 18.04.2013 | Germany | | MemberState | 4 |

| |
|---|
| <p>Comment received</p> <p>Substance identity: The stated substance which should be classified is Phenol, dodecyl branched (CAS-Nr. 121158-58-5). However the given detailed identity stated a content of 44% (40-60%) for Phenol, dodecyl branched, and relative high amounts of C11 (14.2%), C13 (14.0%) and C14 (7.8%) of the alkylchain. Therefore the substance should better be named Phenol, C11-C14 branched, so that more constituents are covered.</p> <p>Furthermore the stated name of the CLH Dossier on the cover page, Part A and Part B of the report is Phenol, dodecyl-, branched with the CAS-No.: 121158-58-5 and EC-No.: 310-154-3. However in the report references are made to the substance Phenol, (tetrapropenyl) derivates (CAS-Nr. 74499-35-7). Furthermore the name Tetrapropenylphenol (TPP) is also stated in Part B as identifier of the substance. Both substances are UVCB substances in which Phenol, dodecyl branched covers substances which have a C12 Alkylchain in ortho, meta or para position at the Phenolring, whereas "Phenol, (tetrapropenyl) derivates" covers substances with four propenyl substituents at the Phenolring and substances with a C12 alkylchain. Additionally in chapter 1.1 of the CLH Report two alternative identifiers are stated: Phenol, dodecyl (CAS-Nr. 27193-86-6) Phenol, 4-dodecyl (CAS-Nr. 104-43-8)</p> <p>Due to the conflict between the given identifiers (name, CAS and EC Nr.) and the detailed identity of the substance, it is not clear which substance should be classified and labeled. Should it be Phenol, dodecyl branched (CAS-Nr. 121158-58-5) or better a substance like Phenol, C11-C14 branched which covers better the given detailed composition. Furthermore please clarify if the substances Phenol, (tetrapropenyl) derivates (CAS-Nr. 74499-35-7) Phenol, dodecyl (CAS-Nr. 27193-86-6) Phenol, 4-dodecyl (CAS-Nr. 104-43-8) because they are used as equivalent identifier or stated as alternative identifier in the CLH Report.</p> <p>Additionally we like to indicate that the detailed composition of the two CLH Dossiers for Phenol, dodecyl branched (CAS-Nr. 121158-58-5) are different.</p> <p>Labelling: p.9 and p.17: It should be noted that Precautionary Statement P337+P313 is missing (indicated by the results of the eye irritation section).</p> |
|---|

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|---|
| Dossier Submitter's Response |
| <p>Substance Identity: We agree the substance identity is complex, and it historically has been identified with different descriptors that can create confusion. Simply stated: the substance is a UVCB (Unknown or Variable composition, Complex reaction products or Biological materials). It is comprised of a distribution of primarily C10-C15 branched alkylphenols. Since this substance is a UVCB substance, we agree a more descriptive name using current</p> |

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nomenclature guidance for UVCBs would be most helpful for clear hazard communication.

The substance is not only complex, as identified, but historical chemical nomenclature guidance and inability to correct inventory nomenclature resulted in a variety of names to describe the same UVCB substance – i.e., a substance manufactured from the same starting reactants. The “dodecyl” reference was in simple recognition that the majority carbon distribution of this UVCB alkylphenol comprised a majority C12 saturated carbon chain. When one applies more recent nomenclature guidance, the same substance has been described as “Phenol, (tetrapropenyl) derivatives” (CASRN 74499-35-7) which allows a more precise description of the UVCB alkylphenol based on the more specifically defined raw materials used for its manufacture. The raw materials are phenol and an olefin commonly known as “Tetrapropylene” or “Propylene tetramer”.

The nomenclature and sameness were discussed at length and agreed among the SIEF and ATC Task Force Consortium members including the lead registrant who has also submitted a CLH dossier for this substance. The SIEF membership concluded that none of the historical names were sufficiently precise or appropriate given current nomenclature guidance, particularly UVCB substances. It is our understanding that other manufacturers of this substance use the same raw materials and manufacturing processes. While typical constituent values may vary, the same constituents are expected to be present. It is also important to note that the test data Oronite submitted for substances described as “TPP” were conducted on samples of the substance representative of the description Oronite provided in the CLH dossier. The key variations between sources will relate to the molecular weight and degree of branching of the alkyl group. The positioning of the alkyl chain on the phenol will be predominantly “para,” but other positions are possible.

The chemical name that was collectively proposed by the SIEF going forward, which reflects the manufacture of TPP more precisely (and for which Oronite is not at liberty to change elsewhere), is: “phenol, alkylation products with C10-C15+ branched olefins derived from propylene tetramer manufacture”.

Chevron’s CLH dossier states: “The identifiers “Tetrapropenyl phenol” and “TPP” are commonly used to describe this UVCB substance. The term “TPP” is used throughout this report and should be considered equivalent to Phenol, dodecyl, branched. These terms have been recognized as equivalent in the OECD ICCA SIAR/SIAP (SIAM 22, Paris, April 18-21, 2006) dossier for this UVCB substance, and the chemical identities have been agreed among the SIEF for EC 310-154-3. Alternative identifiers for this same substance are commonly used. The most common identifier is CASRN 74499-35-7; Phenol, (tetrapropenyl) derivatives. This CASRN is not listed on the EINECS inventory, and most manufacturers have used the descriptor CASRN 121158-58-5 to identify their substances.”

The additional CASRNs listed as alternative identifiers are included in the CLH reports since they are referenced in the OECD SIAR/SIAP dossier for this UVCB substance:

- Phenol, (tetrapropenyl) derivatives (CAS-Nr. 74499-35-7)
- Phenol, dodecyl (CAS-Nr. 27193-86-6)
- Phenol, 4-dodecyl (CAS-Nr. 104-43-8)

As stated earlier in this response, the CASRN 74499-35-7 is the most common identifier used for this UVCB substance globally, and this CASRN is considered the same substance as the CLH Dossier substance. The other CASRN identifiers do not carry UVCB names, so they are not as specific and are less likely to be the same substance according to today’s standards for the naming of substances.

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In an earlier consultation with ECHA just prior to the submission of our CLH Proposal, we discussed both the manufacture and composition of this alkylphenol in more detail. A summary of these discussion points is included below.

In general, the industry manufacturers of TPP (of which Oronite is aware) manufacture TPP using two primary raw materials: Phenol and an olefin commonly known as “Tetrapropylene”, also known as “Propylene Tetramer”. As the name implies, this tetramer originates via the acid catalyzed oligomerization of propene, and the crude olefin (“tetramer”) consists of an array of oligomers primarily including dimers, trimers, tetramers, pentamers, and hexamers. This crude composition is then refined by distillation to obtain a narrower range of olefin homologs wherein the majority molecular weight corresponds with a C12 rich highly branched olefin. Oronite uses polyphosphoric acid to catalyze this oligomerization whereas others use solid Lewis Acid catalysts for the same purpose. The subsequent distillation of crude “tetramer” can result in differing amounts of the higher C15 oligomer, and trace amounts of the C9 trimer are also usually present. All producers of TPP that we are aware of use “Propylene Tetramer”, as defined herein for this purpose, which is in and of itself a UVCB substance. The SIEF did not identify any producers of TPP that use 1-decene, iso-decene, or any other substantially linear C12 olefin for this purpose.

The next and final step in TPP manufacture involves the Lewis Acid catalyzed alkylation of phenol itself. In our experience, preferred catalysts are of the Amberlist sulfonic acid resin variety using a heated plug through reactor. To control the degree of alkylation, a large excess of phenol is used which results in typically greater than 95% mono alkylation. Because the structural nature of the highly branched olefin composition and the reaction conditions employed, this alkylation proceeds under thermodynamic control affording typically greater than 90% para substitution. Excess unreacted phenol and unusually low molecular weight alkylates are then exhaustively removed by distillation resulting in TPP in commercially useable purity. Ortho alkylphenol and dialkylated phenol are also observed as minor impurities.

While “Tetramer” typically reflects its propene chemical starting materials in so far as the dominate oligomers seen are multiples of three, the ensuing alkylation of phenol by acid catalysis produces a different but not unexpected result. Purified TPP typically exhibits a more or less bell shaped modal distribution covering the entire single carbon homolog range possible. This means that over the range of C9-15+ alkylphenol, C10, C11, C12, C13, C14, C15, and C15+ can be detected in proportions that no longer reflect their C3 oligomeric origins. The C12 isomeric cluster of alkylphenols still dominates the composition, but it is clear that Lewis Acid alkylation conditions also promote alky cleavage reactions at the same time. Though the breadth of this distribution may vary from one producer to the next, a singular modality is nonetheless observed. This is why, at the SIEF level of information exchange, we had agreed the current proposed name for TPP, which reflects the C10-15+ range observed.

Labelling:

Skin irritation was not included in Oronite’s CLH Dossier since only the reproductive toxicity endpoint was identified as having differences among registrants.

RAC’s response

Thanks you for your comment.

| Date | Country | Organisation | Type of Organisation | Comment number |
|--|-------------|-------------------|----------------------|----------------|
| 26.03.2013 | Switzerland | SI Group-UK, Ltd. | Company-Manufacturer | 5 |
| Comment received | | | | |
| We believe that the existing data supports the classification of PDDP as Repr. Cat. 2 H361 f (CLP Regulation). A detailed evaluation of all the hazard endpoints was provided in the first industry CLH dossier submitted for Phenol, dodecyl-, branched [Tetrapropenylphenol (TPP)] | | | | |

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corresponding to the classification and labelling proposed in the REACH joint registration dossier and as supported by the majority of the members of the SIEF. The public consultation period for this dossier has already finished and the dossier submitter has provided extensive responses to all the comments received during public consultation in the respective RCOM tables.

Dossier Submitter's Response

Commenter 5 did not provide their responses to all comments received during their public consultation period, and thus we are not in a position to evaluate them.

Our interpretation of the reproductive toxicity data aligns with the interpretations of the study directors: some reproductive effects appear to be independent of systemic effects and thus the substance should be classified as Repr 1B. The first CLH dossier was initially submitted to ECHA prior to availability of the final report for the two-generation reproduction study, which was issued in May 2012. The study director's interpretation of the reproductive effects:

"Tetrapropenyl phenol (TPP) administered at a dietary level of 75 mg/kg/day elicited a number of effects on body weights, food consumption, estrous cyclicity, reproductive performance, and developmental parameters. Adverse effects upon reproductive parameters were interpreted as direct effects upon the reproductive system and not a secondary consequence of generalized systemic toxicity." (Edwards, 2012; page 132)

The range of comments received by the first industry CLH dossier submission, in addition to those submitted in response to this submission, mirror the complexity of the data for this substance. We acknowledge that this is a complicated toxicological issue.

RAC's response

The option of classification of TPP as Repr. 2 was considered by RAC; however, classification as Repr. 1B was considered justified based on the information provided to RAC. The rationale and justification for the classification as Repr. 1B is contained in the opinion document.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---------|--------------|----------------------|----------------|
| 18.04.2013 | France | | MemberState | 6 |
| Comment received | | | | |
| FR agrees with the classification proposal for toxicity for reproduction in category 1B for fertility. We also agree with the SCL proposed. | | | | |
| Dossier Submitter's Response | | | | |
| We agree with Comment 6. Thank you for your review. | | | | |
| RAC's response | | | | |
| Thank you for your view which is supported by RAC, except for the SCLs (see RAC response to comment No. 2). | | | | |

TOXICITY TO REPRODUCTION

| Date | Country | Organisation | Type of Organisation | Comment number |
|------------------|---------|--------------|-------------------------|----------------|
| 19.04.2013 | France | | Company-Downstream user | 7 |
| Comment received | | | | |

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON PHENOL, DODECYL-, BRANCHED [TETRAPROPENYLPHENOL (TPP)]

The dossier submitter proposes classification of TPP as toxic for reproduction category 1B based on effects which, according to his expert judgement, provide a clear evidence of adverse reproductive effects which cannot be fully explained by the general toxicity of the substance.

We disagree with this position and consider that most effects have been observed in the presence of a toxicity that, with the information available, can probably be considered as strong if not excessive. In this context we consider that a category 2 is more appropriate. Indeed, the Guidance on the Application of the CLP Criteria states that "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". Therefore, according to the regulation, even if the effects can only partially be explained by the general toxicity, category 2 can still be applicable.

For this substance, if we consider the main study: the 2-generation study which is the most complete and which has been conducted using a relatively relevant route of exposure (compared to gavage in which bolus administration may provide excessive peak concentration), it appears, with the information available in the CLH report, that top dose was probably excessive. As a matter of fact in the F0 generation a 12% BW decrease was observed in females at termination. If we consider that the study started with female rat's body weight (BW) of about 220-260 grams, the decrease in body weight gain (BWG) was in the range of 50% or more which, we think, is excessive. This relative decrease is probably even more important in the F1 female where 256 g at initiation of mating is in the same range as expected BW around 10 weeks while these animals were probably around 18 to 20 weeks if we consider female control's BW (293 grams).

It is stated in the Guidance on the Application of the CLP Criteria that "There is no established relationship fertility effects and less marked systemic toxicity (than lethality, dramatic reduction of actual body weight, coma)". This is not absolutely correct for several fertility parameters especially in rodents. Rodent must cope with transient changes in food availability. Their optimal coping strategy which is well documented is a rapid cessation of breeding associated with a reduction in energy devoted to reproduction and other non-essential process. Nutritional infertility is the result of different factors like a decrease in GnRH (Kriegsfeld et al. 2001) or Ghrelin (Ahmed et al. 2012) release and probably with other more peripheral processes like a decrease in estrogenic receptors (ES) (Jones et Wade 2002) or suppression of pulsatile LH release (Nagatani, Tsukamura, et Maeda 1994). These changes, although rapidly reversible when food deprivation is not too pronounced, will obviously modify several of the fertility parameters measured in reproduction studies. A number of publications have dealt with the relationship between food restriction and different aspects of the reproductive performance. Some of these publications have been used to assess whether the general effects as those reported in this study, essentially the BW changes, were sufficient to explain the reproductive effects. On this basis, the submitter paper, as well as other commenters, conclude that this was not the case, and then that these effects should be considered as specific reproductive effects. They have especially looked at the relationship between decreased BWG (or absolute BW) and effects. However, this type of data should be interpreted with caution as rat, especially SD are prone to obesity when fed ad libitum; a decreased BW when control is obese will have different effects than a decreased BW versus a non-obese control. In addition, decreased BW gain may be only one of the unspecific expressions of general toxicity and therefore, decreased BWG due to food restriction may not be the perfect model to study decreased BWG due to general toxicity.

Most of the effects on reproduction described in the 2-generation study as well as in the other studies conducted with this substance have also been observed at different degree in food deprivation studies. Decreased BWG in the dam may induce a decrease in ovary weight and number of corpora lutea (Terry et al. 2005; Seki et al. 1997; Chapin et al. 1993),

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increase oestrus cycle length (Terry et al. 2005; Seki et al. 1997) and in general decrease global reproductive performance (Guzman 2006; E. Zambrano et al. 2005; Aiguo Wu et al. 2002). For example, KK Terry et al (2005) reported on compromised fertility due to reduction in corpora lutea associated with a 16% BW decrease which is not far from those reported in this study (Terry et al. 2005).

In the males testis weight has been found to be decreased (E. Zambrano et al. 2005; Sirotkin et al. 2008)(11, 12) or without changes (Chapin et al. 1993; Fan et al. 1997) together with Leydig cells atrophy (Seki et al. 1997) which is probably the consequence of LH (Ahmed et al. 2012; Fan et al. 1997) and testosterone (Levay et al. 2010; Rehm et al. 2008; Chapin et al. 1993) secretion decrease. Epididymis (Rehm et al. 2008) as well as prostate weight (Rehm et al. 2008; Rocha et al. 2007) and sperm concentration and mobility (Aiguo Wu et al. 2002; Fan et al. 1997) can also be decreased. This may be especially the case in the F1 generation which have been exposed to dietary restriction during foetal development (Toledo et al. 2011) and this should contribute to decreased general reproductive performance.

Food restriction may also increase corticosterone (Guzman 2006; Levay et al. 2010; E. Zambrano et al. 2005) which is a major hormone to maintain carbohydrate metabolism and will then play a major role to maintain homeostasis despite this food restriction; this may be the explanation for the increased adrenal weight reported with this substance and this contribute to think that this general toxicity was sufficiently severe to impact the hormonal regulation.

In summary there are a number of effects reported in this 2-generation study which impact the reproductive system and could suggest either a consequence of the decreased BWG or a hormonal effect, especially an estrogenic effect. This last effect being also more suggested by the vaginal patency which occurred at a younger age while food restriction would have better explained a delayed sexual maturation and the mechanistic studies which tend to demonstrate that the substance could have a weak estrogenic effect in vivo and in vitro. However, the picture is far to be consistent with a specific effect:

- 1> The early sexual maturation was apparently not observed in the F2 offspring
- 2> There was also no modification of the anogenital distance in either sex which would have been expected in case of an estrogenic effect
- 3> There were apparently no effects in reproductive organs in the dog at much higher dosage (200 mg/kg bw/day) over 13 weeks.

There is then no clear evidence that the adverse effects seen on sexual function and fertility are unrelated to the general toxicity observed in this study at the top dose (and at the mid dose in the F1 generation). A large part of these effects can be explained by the decrease BWG and the general toxicity which has induced it. Although some of these effects could go in the direction of an estrogenic effect, the picture is not really consistent with such a specific effect.

However, as some of these effects may not be completely explained by general toxicity, the picture is clearly fitting with the criteria of Category 2 classification for reproduction:

- There is some evidence from one experimental animal (but not in a second species) of an adverse effect on sexual function and fertility
- These effects have been observed together with other toxic effects and it is difficult to evaluate exactly the contribution of this general toxicity to these effects.
- There is no consistent picture of a specific effect to provide a sufficient evidence to propose a category 1 classification.

Literature

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Dossier Submitter's Response

We thank Commenter 7 for the thorough review and provision of references.

- With regard to the consideration of excessive toxicity observed in the high exposure levels of the TPP studies and the potential for excessive systemic toxicity to produce effects upon the reproductive system:
 - Males: The CLH dossier submission provided literature citations that evaluated the relationship between decrements in body weight resulting from food restriction and changes to reproductive organs. We reviewed these references and provided them in our dossier as a comparison to the changes observed in TPP studies to body weight and in the reproductive organs. The general pattern observed in male rats, both feed restriction studies and in the TPP reproduction and repeated-exposure studies, was a decrement in accessory reproductive organ weights relatively commensurate with the decrement to body weight. We do not have a clear understanding of whether male reproductive changes observed at the highest TPP dose levels are strictly secondary to body weight changes or are partly a consequence of direct effects. In our interpretation of the TPP data for systemic toxicity, specifically as measured by changes to body weight or body weight gain in male rats, the decrements to male body weight produced by TPP are of sufficient magnitude to prevent a clear interpretation of male reproductive toxicity. Male rats were generally more sensitive than female rats to TPP-induced adverse systemic effects.
 - Females: In contrast to data for male rats, the mild to moderate body weight decrements observed in female rats in the TPP studies were insufficient to account for effects to ovaries or female reproductive function. Data for females and offspring are provided in our response to Comment 3. At the initiation of mating in the two-generation reproduction study, F0 females were smaller than the F0 female control rats by 12.5% and 29.6% in body weight and body weight gain, respectively. For F1 females, the differences were 12.6% and 11.6%, respectively, for the same parameters. These decrements (by themselves) do not fall into the range of body weight/gain decrements that affect reproductive organ weights or functional changes in reproduction. Feed restriction studies conducted with Sprague-Dawley rats (Chapin, et. al, 1993) indicate that a 20% decrement in body weight produced no effects to female reproduction, whereas a 30% decrement in body weight adversely affected female reproduction.
- We agree with Commenter 7 that rapid, severe body weight effects from nutritional restriction studies support the concept that adverse reproductive effects may occur in rodents as secondary effects to the toxicity upon general health and growth. We also agree that there is variability in the responsiveness of reproductive function secondary to nutritional deprivation, as noted by the references provided in the Comment. As reported in several of the references provided by Commenter 7, severe feed restriction adversely affects fertility in rats, and mice are more susceptible to these effects. However, that is not what was found in the TPP studies at the lower dose levels. We agree that use of body weight as a measure of general toxicity to interpret reproductive toxicity may not be a perfect model; however, it may be the most appropriate model for interpretation of the TPP results. References as provided by the commenter were

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reviewed prior to our self-classification decision; our interpretation aligns with that of the study directors – that the studies provide evidence of direct reproductive effects.

- With regard to an absence of effect upon vaginal opening in the F2 offspring: F2 and F2a offspring were not evaluated for sexual maturation.
- With regard to anogenital distance (AGD): Although AGD is a measurement triggered by changes to timing of sexual maturation, we are unaware that it is consistently more sensitive, or as sensitive, as sexual maturation. We do not believe that a change in timing of sexual maturation should be ignored if changes to AGD do not occur also.
- With regard to the absence of effects in the dog at higher dose levels: As the dog study used very small numbers of animals (n = 3) and was not designed to provide a thorough evaluation of either reproductive or systemic toxicity as was performed in the rat reproduction studies, the absence of statistically significant findings in the dog is inconclusive. This point would warrant further consideration if Commenter 7 could provide empirical evidence that the toxicokinetics for TPP in the dog are more relevant to the human than the rat.

RAC's response

The data supporting classification Repr. 1B, H360F according to the CLP Regulation, provide clear evidence from animal studies of an adverse effect of TPP on sexual function and fertility occurring together with other toxic effects, but the adverse effects on fertility are not considered to be secondary non-specific consequences of other toxic effects.

| Date | Country | Organisation | Type of Organisation | Comment number |
|------------|---------|--------------|----------------------|----------------|
| 19.04.2013 | Sweden | | MemberState | 8 |

Comment received

Comments have been submitted as an attachment.

(ECHA note: The attachment provided is copied below)

Reproductive toxicity :

The Swedish CA supports the proposed classification as repro 1B for Phenol, dodecyl-, branched (CAS no 121158-58-5). The dataset submitted for this dossier partly overlap with the dataset that we reviewed during public consultation for another dossier regarding phenol, dodecyl, branched earlier this year and therefore the Swedish CA want to reuse the comments that we provided at that time on this endpoint (see below under heading "Comments submitted...").

The present dossier also contains data from female pubertal assays, uterotrophic assays and from in vitro androgen/estrogen binding assays (that were not available with the previous dossier). Together, the results from these assays bring additional evidence that phenol, dodecyl, branched disturbs the endocrine system in adult and immature rats. The addition of this dataset therefore justifies a classification in category 1B regarding effects on fertility, which also was proposed by the dossier submitter.

We are aware of the fact that section 3.7.1.3 in Annex I of the CLP legislation indicates that effects on onset of puberty should be viewed as effects on sexual function and fertility, but we are of the opinion that onset of puberty could be viewed as an effect on a developmental process that will have impacts on sexual function and fertility. Therefore we think that it would be too stringent to classify and label this effect strictly as an effect on fertility especially since it also was observed in the 2 gen reproductive toxicity study. Instead we suggest that one use the option given in the CLP legislation (Annex VI, section 1.2.3, first para) to only use H360 without specification of D and F in situations (like the present one) where there is a general concern for effects on fertility and/or development.

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The present dossier suggests a specific concentration limit (SCL) of 1.5%. It is unclear how the dossier submitter has arrived at this figure and without a transparent description on how a NOAEL of 15 mg/kg bodyweight is transferred into a SCL of 1.5% we think it is more appropriate to use the generic concentration limit of 0.3%, which would be in line with the instructions given in table 3.7.2.5.5 in the CLP guidance document.

Comments submitted in February 2013 regarding reproductive toxicity of phenol, dodecyl, branched
Reproductive toxicity

The Swedish CA supports the proposed classification of Phenol, dodecyl-, branched / Phenol, (tetrapropenyl) derivatives (CAS nr 121158-58-5, 74499-35-7) as a reproductive toxicant in category 2 regarding effects on fertility. In addition we propose that it also should be classified for developmental toxicity (category 2) and for effects via lactation.

Developmental toxicity

In an OECD guideline 414 study, two fetus (from different litters) with ectrodactyly were found in the high dose group. One of these fetuses also had brachydactyly and absent claw. In addition a low incidence of malformations affecting the humerus, ulna, radius or femur were also recorded and a number of fetuses (10) displayed the malformation "scapula/scapular spine curved" at the highest dose level (300 mg/kg). Data is lacking that clarifies the number of fetuses that were affected by one or more of these malformations. In addition, decreased litter size (8.9 as compared to 12.5 in controls) and a decreased fetal weigh (3.47 as compared to 3.76 g in controls) were also recorded at the high dose level. No similar findings were recorded in the lower dose groups and no historical control data is available.

Maternal toxicity was observed at the 300 mg/kg dose level as decreased bodyweight gain Day 6-15 of (62 % lower than the gain observed for the controls) and decreased food intake (- 18% as compared to the controls). No mortality was recorded at this dose level and the only clinical sign that was recorded was soft stool. Animals at the 300 mg/kg dose level seemed to recoup somewhat after end of dosing, since the decrease in body weight gain was not as dramatic as the one observed during the dosing period (-16% as compared to the controls but most likely the decreased body weight gain is overestimated since the data has not been adjusted for the lower gravid uterus weights that was caused by the resorptions). The maternal toxicity observed at the high dose level can therefore explain the effects on fetal weights and probably also to some degree the increased number of resorptions. However there is no data in the present study that suggest a mechanism that link the observed maternal toxicity to the occurrence of the malformations, and we are not aware of any literature that link the general maternal toxicity as described in this dossier to the occurrence of specific malformations. No evidence of teratogenicity was recorded in the one and two generation studies that were performed at lower dose levels (high dose levels were 125 and 75 mg/kg, respectively).

In summary, we propose that Phenol, dodecyl-, branched / Phenol, (tetrapropenyl) derivatives should be classified as a category 2 reproductive toxicant regarding developmental toxicity. The "signal strength" in the data does not justify a classification in category 1b.

Effects on fertility

Signs of effects on the estrous cycling (increased numbers of females showing persistent diestrus/estrus) were seen in females dosed with 125 mg /kg in the one generation reproductive gavage rat toxicity study. A reduced fertility index was also observed and the mean number of implantations was radically decreased (3.3 as compared to 14.1 in the control group) and consequently the litter size was also much lower as compared to the control litter size. Histopathological examination revealed an increased incidence of females with a decrease in the numbers of corpora lutea and an increased incidence of females having ovary cysts and/or endometrial cysts in high dose females. The weights of the

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ovaries (absolute and relative to body weight or brain) were all statistically significantly decreased in the high dose group. No overt maternal toxicity was evident at time of pairing. During the pre-mating period the high dose females had a lower body weight gain (-21.3 % as compared to the controls) and at time just before mating the mean weight of the high dose females was 9.7% less than the weight of the control females. Interestingly an increased incidence of females with persistent diestrus was also observed in the intermediate (25 mg/kg) dose group (four animals as compared to 16 in the high dose and two in the control). No effects on fertility index or on litter size were observed for this dose group, but again a decrease in the weight of the ovary (absolute and relative to brain) was recorded. At this dose level the pre-mating body weight gain and weight just before mating were similar for the intermediate dose females and the control females. Although no effects on fertility index or on litter size were noted in the females in the two generation dietary reproductive toxicity study, partly similar signs as those observed in the one generation study were observed. The weight of the ovary was reduced (75 mg/kg, F₀ and F₁) and an increased incidence of females with reduced number of corpora lutea (75 mg/kg, F₀ and F₁ females) and of females with ovary cysts (6/30, 13/30 and 10/30 in the control, 15 mg/kg and 75 mg/kg dose group, respectively in the F₀ generation) were observed. Vaginal patency was recorded in F₁ females at an earlier time point (and at a significantly lower mean bodyweight) as compared to the controls. However no similar effect was noted in the one generation study and no effect on the anogenital distance was seen in the F₂ generation. Maternal toxicity was recorded in this study, just before the mating period 75 mg/kg F₀ females weighed 12.6% less than the control females, and on lactation day 21 the difference in bodyweight was ~5% but no effects were observed for the 15 mg/kg F₀ females. The 75 mg/kg F₁ weighed 12.5% less than controls around mating whereas 15 mg/kg F₁ females weighed about the same as the controls around mating. Interestingly, Chapin (Fundamental and Applied Toxicology 20, 23-29, 1993) reported for Sprague Dawley rats that feed restrictions resulting in a weight of 70% of the controls had no effect on fertility. Decreased ovary weights and decreased number of corpora lutea as well as a transient prolongation of the estrous cycle time were seen in female rats that weighed 70% of controls but not in rats that weighed 80 or 90%, i.e. a similar effect on bodyweights as the maximum effects recorded in the present studies.

Table 1. Summary of statistically significant effects of Phenol, dodecyl-, branched on male organ weights

| Organ | Weight | One – generation study (gavage) | | Two - generation study (dietary) | | |
|------------------------|-------------------------|---------------------------------|----------------------|----------------------------------|----------------------|----------------------|
| | | Dose level (mg/kg) | | Dose level (mg/kg) | | |
| | | 125 (F ₀) | 25 (F ₀) | 75 (F ₀) | 75 (F ₁) | 15 (F ₁) |
| Pre-mating body weight | Absolute (% of control) | 79,4 % | 96 % | 82,7 % | 77,5 % | 95,1 % |
| Adrenals | Absolute | ↑ | | | | |
| | (%) | ↑ | | ↑ | ↑ | |
| | (g/100g brain) | | | | | |
| Cauda epididymis | Absolute | ↓ | ↓ | ↓ | ↓ | ↑ |
| | (%) | | | | ↑ | ↑ |
| | (g/100g brain) | ↓ | ↓ | ↓ | | ↑ |
| Epididymis | Absolute | ↓ | | ↓ | ↓ | ↑ |
| | (%) | ↑ | | | ↑ | ↑ |
| | (g/100g brain) | ↓ | | ↓ | | ↑ |
| Prostate | Absolute | ↓ | | ↓ | ↓ | |
| | (%) | | | | ↑ | |

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| | | | | | | |
|-----------------|----------------|---|---|---|---|--|
| | (g/100g brain) | ↓ | | ↓ | | |
| Seminal vesicle | Absolute | ↓ | ↓ | ↓ | ↓ | |
| | (%) | ↓ | | ↓ | ↑ | |
| | (g/100g brain) | ↓ | ↓ | ↓ | ↓ | |
| Testis | Absolute | ↓ | | ↓ | ↓ | |
| | (%) | ↑ | ↑ | ↑ | ↑ | |
| | (g/100g brain) | ↓ | | | | |

As summarized in Table 1, Phenol, dodecyl- branched had an effect on male reproductive organ weights. Effects were observed both in the one- and two-generation reproductive studies. Interestingly effects were also seen at dose levels that caused mild toxicity (as revealed by effects on pre-mating body weights and adrenal weight). Histopathological examination of the reproductive organs revealed no effects in the two- generation study, but in the one-generation study a reduced prostate secretion was observed in all dose groups, a reduced coagulation gland was found in males dosed ≥ 25 mg/kg and reduced seminal vesicle secretion was observed only at the 125 mg/kg dose group. Sperm analysis did not reveal any effects in males in any of the studies.

In summary, effects on male and female reproductive organ weights were observed in the one- and two-generation reproductive toxicity studies. Effects were generally observed at dose levels that caused some toxicity (as revealed by effects on the absolute body weight but no mortalities) but signs of similar effects were also observed at lower dose levels. Estrus cycling was affected in both studies as revealed as a somewhat prolongation of the estrus cycle time or as an increase in the number of females displaying persistent or prolonged diestrus or abnormal estrus. These effects were most pronounced in the high dose groups but effects were also recorded at lower dose levels. Decreased number of corpora lutea (high dose groups, F₀ and F₁) and an increase in the number of females with ovary cysts were also observed. Overall no effect on sperm function was recorded. A significant decreased fertility was also recorded in the one generation study at the high dose level in combination with clear toxicity (but no mortalities). These effects indicate that the test compound can perturb the endocrine system and that at high dose levels this perturbation will affect fertility. A classification of phenol, dodecyl-, branched as a category 2 reproductive toxicant regarding effects on male and female fertility is therefore warranted.

Effects on or via lactation

In the two generation dietary study, five F₁ (sex distribution not specified in the report) animals in the high dose group (75mg/kg) were found dead or killed just after weaning due to their poor condition. Death occurred in animals with low body weight. In addition, an effect on pup weight was also a general phenomenon in this study and it was most pronounced in the F₁ generation. On day 1 the mean weights of the F₁ high dose pups were similar to the controls (96% [males] and 97% [females]) but on day 21, males weighed 28% less and females 30% less than the controls. During lactation maternal toxicity (as revealed by effects on maternal body weight) was minimal. The weight of the phenol, dodecyl treated dams at end of lactation (day 21) was only minimally lower (5.2%) as compared to the control group and the treated high dose dams actually gained more in weight during lactation (43 g) as compared to the control dams (25 g). In addition the influence of the mild maternal toxicity (the high dose dams weighed $\sim 10\%$ less on gestation day 20) that was observed during pregnancy at this dose level seemed to have had a negligible effect on the pups since there was no effect on pup survival or pup weight on day 1. In summary, the observed detrimental effect on pup growth justifies a classification for effects via lactation and thus the addition of H362.

---- End of attachment ----

Dossier Submitter's Response

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON PHENOL, DODECYL-, BRANCHED [TETRAPROPENYLPHENOL (TPP)]

We wish to clarify that data from the additional assays (female pubertal, uterotrophic, and receptor binding) were provided to other registrants from 2011 through 2012. In late 2011, registrants were advised that we had new data, and these findings were summarized. In early 2012, we provided Robust Study Summaries of each new study, and these were subsequently revised at the behest of the TPP Task Force membership shortly afterwards. In mid 2012, we made available to this membership our full CLH proposal. Later that year, we provided complete copies of each new study report for anyone in the Task Force to review. The Lead Registrant for TPP agreed subsequently to update the TPP REACH dossier accordingly. In late 2012, the updated dossier was submitted through REACH IT. In addition, the final report for the two-generation reproductive toxicity study (Edwards, *et al.*, 2012) was issued several weeks after the other dossier by the Lead Registrant was prepared and initially submitted.

- With regard to the onset of puberty as a developmental effect: Sexual maturation, manifested by vaginal opening, was accelerated in female offspring (F1) in the two-generation study at 75 mg/kg/day in which direct dosing of the offspring likely began prior to weaning through consumption of the diet; sexual maturation was not measured in the F2 offspring. Sexual maturation was unaffected in the one-generation reproduction study, in which the offspring retained for evaluation of vaginal opening were not dosed (gavage) after weaning and were not directly dosed during the lactation period. In the one-generation study, direct dosing was not undertaken in order to determine if timing of puberty would be altered as a result of prenatal or lactational exposures.
- With regard to the Specific Concentration Limit (SCL) of 1.5 wt.% Determination: Self-classification utilizing the SCL of 1.5 wt.% was initially (2010) based upon the considerations that:
 - (i) The SCL should differentiate substances and mixtures that, if tested according to accepted regulatory test guidelines, would be anticipated to produce a reproductive finding based upon TPP content. 15 mg/kg/day is equivalent to 1.5 % of the OECD Test Guideline 416 limit dose of 1000 mg/kg/day. The test guideline indicates that 1000 mg/kg/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.*" (paragraph 16, OECD Test Guideline 416, adopted 22 January 2001; http://www.oecd-ilibrary.org/docserver/download/9741601e.pdf?expires=1367794963&id=id&accn_ame=guest&checksum=05A881A766A1858623A7713EAF98AD53). Due to the physical chemical properties of TPP (high viscosity, very low volatility) and use (manufacturing intermediate for additive packages and engine oils), we have no reason to believe that human exposure would warrant a higher potential test dose than 1000 mg/kg/day. Skin contact is the most likely route of human exposure (occupational); however, the test substance is a skin irritant and would present animal welfare concerns if tested for reproductive toxicity by this route. Recent dermal penetration test data have indicated that only approximately 3% of an applied dose is likely to be absorbed through human skin. Consequently, due to low dermal absorption and the absence of significant exposure by other routes, the limit dose of 1000 mg/kg/day was a reasonable maximum dose.
 - (ii) Further supporting low exposure potential are the exposure assessments conducted for the TPP Chemical Safety Report (CSR). The predicted dermal exposure to TPP for workers, determined using the ECETOC TRA tool (www.ecetoc.org), demonstrates that the exposure potential is extremely low. In addition, the exposure assessment found in the CSR of a representative lubricating additive that contains TPP as an impurity, Phenol, dodecyl-, sulfurized,

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carbonates, calcium salts, overbased (EC Number 272-234-3), also demonstrates negligible exposure potential to workers, professionals, and consumers. Specifically, sections 10.1-10.6 of the CSR employ a tier 1 exposure assessment using the ECETOC TRA tool to predict dermal exposure to workers and professional users; appendix 4 of the CSR provides detailed calculations on how the modified (e.g., with exposure controls) exposure estimates were obtained. Sections 10.7 and 10.8 of the CSR use ConsExpo (v 4.1) to predict dermal and oral consumer exposures. As an example, the maximum predicted dermal exposure to the additive Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased, after applying modifying factors (from the CEFIC CSA tool with ATIEL-ATC use groups, v1.0), is 1.1 mg/kg/day. To calculate the amount of TPP as absorbed dose from this representative lubricating additive, the amount of residual TPP (6.7 wt.% of the additive) and the expected dermal absorption of TPP (3%) must be factored in and results in 0.002 mg/kg/day TPP (1.1 mg/kg/day * 6.7% * 3.0%). This is 750-fold lower than the NOAEL (15 mg/kg/day TPP) used to establish an SCL used for self-classification. This demonstrates that the exposure potential is extremely low, and thus, the test guideline limit dose of 1000 mg/kg/day is sufficient for testing and classification.

- (iii) The SCL was validated against the test data for four reproductive toxicity studies conducted with TPP-derived substances. These studies were pre-existing and enabled us to avoid additional animal testing. The concentration of TPP in these test substances ranged from 2.5 wt.% to 26 wt.% TPP, with tested dose levels of 1.25 mg TPP/kg/day to 67 mg TPP/kg/day. There were no effects upon TPP-responsive reproductive parameters in these studies at dosage levels below 15 mg/kg/day. Test substances that contain more than 1.5 wt.% TPP are currently self-classified Repr. 1B.
- (iv) Subsequent to the initial SCL determination, draft guidance was published by ECHA based upon an approach derived from calculation of the ED10. Use of the LED10, the lower confidence interval value for the ED10, derived a slightly higher value, 1.86% (18.6 mg TPP/kg/day), than the SCL determined by the NOAEL method. We opted to use the empirically derived value. The existence of multiple sets of empirical data that ≤ 15 mg/kg/day does not result in TPP-derived reproductive toxicity is sufficient evidence to establish the SCL. The use of the default banding approach recommended for General Concentration Limit (GCL) determination is unwarranted for this substance.
- Additional LED10 values were also calculated from the two-generation and one-generation reproduction studies, and the 90-day study:
 - Ovaries: 18.6 – 53.8 mg TPP/kg/day
 - Litter Size: 34.2 – 67.6 mg TPP/kg/day
 - Implantation Number: 25.8 – 64.7 mg TPP/kg/day
- (v) The current guidance for SCL determination states that an SCL may be set by a manufacturer, importer, or downstream user where there is adequate, reliable, and conclusive scientific information that a hazard of a classified substance is not evident at a level above the generic concentration limit. TPP presents an exceptional circumstance in which two reproduction studies exist for the classified substance and multiple reproductive toxicity studies exist for TPP-containing substances. We believe this to meet the scientific standard stated in the draft guidance and to be protective of human health. (http://echa.europa.eu/documents/10162/13562/clp_en.pdf)

Response to comments submitted in February 2013:

- With regard to developmental toxicity: The developmental toxicity report does not provide sufficient information about maternal parameters to understand the potential

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relationship between maternal and developmental toxicity in this study. One of the developmental observations noted in the study, wavy ribs, is no longer considered a malformation but a developmental variant common with maternal health effects. Regarding malformations of the scapula or limb bones, we note that similar findings were not noted in the rat reproduction studies despite thorough weekly observations of the offspring. We also note that the dose level associated with the finding in the developmental toxicity study, 300 mg/kg/day, is a dose level that produced a 20% decrease in body weight in females in the 28-day study, a level of effect that exceeds the usual target of approximately 10% body weight difference for maternal toxicity. An initial dose of 500 mg/kg/day was terminated due to excessive (31%) maternal mortality.

- With regard to effects on fertility: We concur that there are similarities between the results of the two-generation and one-generation rat reproduction studies.
 - Table 1 provided by the commenter: The commenter indicates that weights of the cauda epididymis and epididymis were increased at 15 mg/kg/day in the F1 males of the two-generation study. These were not considered to be effects of treatment because the differences occurred only to the left side – there was no evidence of an effect upon the right side. In fact, the control weights for the left side were approximately 10% lighter than the right side:
 - Control: Left Cauda Epididymis: 0.3028 g
 - Control: Right Cauda Epididymis: 0.3349 g
 - Control: Left Epididymis: 0.67 g
 - Control: Right Epididymis: 0.76 gOrgan weight differences are considered to be a more sensitive indicator of effects to the male reproductive organs as weight is not a subjective evaluation (Everds, NE, PW Snyder, KL Bailey, B Bolon, DM Creasy, GL Foley, TJ Rosol, and T Sellers. <http://tpx.sagepub.com/content/early/2013/03/01/0192623312466452>) Interpreting stress responses during routine toxicity studies: a review of the biology, impact, and assessment. Toxicol. Pathol. (2013). Effects upon fertility associated with changes to estrous cyclicity were clearly evident at 125 mg/kg/day and minimally observed at 75 mg/kg/day, but not apparent at 25 mg/kg/day and lower doses.
- With regard to effects on or via lactation: We have not classified TPP for effects on or via lactation because we do not believe that there is sufficient evidence for this classification:
 - (a) There is no human evidence indicating a hazard to babies during lactation;
 - (b) There is no evidence of adverse effects to the offspring due to milk quality or transfer of this substance into milk;
 - (c) We have no evidence of transfer of TPP into milk, and consequently also no evidence of potentially toxic levels in milk

RAC's response

1. The support for classification of TPP as Repr.1B has been noted.
2. Classification for developmental toxicity was not supported by RAC because the maternal toxicity was considered greater than the observed fetal toxicity. Therefore the existing data do not warrant classification of TPP as a developmental toxicant.
3. Classification for effects on or via lactation was not supported by RAC since the observed effects do not meet the CLP classification criteria for this category.
4. The calculations of the concentration limits in the RAC opinion are based on based on the new Guidance on the application of the CLP criteria (Version 4.0 – November 2013, section 3.7.2.5. Setting of specific concentration limits). For medium potency substances, such as

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| TPP, the GCL should be used, namely 0.3 % for substances classified as Repr. 1B according to the CLP Regulation. | | | | |
|---|-------------|--------------|----------------------|----------------|
| Date | Country | Organisation | Type of Organisation | Comment number |
| 09.04.2013 | Netherlands | RIVM | National Authority | 9 |
| Comment received | | | | |
| <p>1. We agree with classification of Repr 1B; H360F, as it is convincing that the bodyweight loss is insufficient to account for the found organ weight losses. Please change H360f into H360F in line with CLP Annex VI paragraph 1.1.2.1.2.</p> <p>2. We do not agree that the self-classification of Repr Cat 1B should not be not based on test data for males (p51-52). Decreases in the weight of male reproductive organs cannot always be attributed to a decreased body weight gain. A large difference in reduction between terminal weight and reproductive organ weights was observed in the 28-d gavage rat study and 90-d rat study. The 28-d repeated dose studies showed a reduction in terminal body weight of up to 13%, while the weights of seminal vesicles, prostate and epididymides at the same dose group were reduced with at least 50% as compared to control animals (Harriman, 2004). The 90-d rat study from Haas (2007) revealed a reduction in male body weight of 35% in the highest dose group, while the prostate weight and seminal vesicle weight were reduced with 78-83%. This effect was also observed in the one-generation study, where body weight was reduced with 28% in males and the seminal vesicle weight and prostate weight were reduced with 44 and 36% respectively (see also Proposal for Harmonised Classification and Labelling of Phenol, dodecyl, branched from SI-Group UK, Ltd, 10 October 2012).</p> <p>Several publications have examined the relationship between body weight changes on organ weight data in the rat (Scharer, 1977; Chapin et al, 1993; Levin et al, 1993; Keenan et al, 1994; Seki et al, 1997; Odum et al, 2001; Marty et al, 2003; Carney et al, 2004; Terry et al, 2005; Laws et al, 2007 as summarized in OECD draft guidance document 151 (http://www.oecd.org/env/ehs/testing/GD%20151_Oct%202012_clean2.pdf)). These studies showed that reductions in the weights of testes and epididymides were lower than reductions in body weight. A 15% body weight reduction was correlated with a testes and epididymides weights reduction of 2-12%; a 40% body weight reduction resulted in testes and epididymides weights being reduced by 24%. Prostate and seminal vesicle weight varied more with body weight. At 10% body weight reduction, prostate and seminal vesicle weights were reduced 0-20% and at 40% body weight reduction, prostate and seminal vesicle weights were reduced 20-45%.</p> <p>These data show that the reduction in reproductive organ weights cannot be fully attributed to reductions in body weight. However, also some other toxic effects were observed in males at dose levels also inducing effects on the male reproductive organs. This includes an increase in adrenal weight. As the adrenal has several functions it is unclear whether the change is related to changes in sexual hormones or other hormone systems. Further, some clinical effects were observed. However, they are unlikely to be the cause of the effects on sexual function and fertility. Overall the available data suggests that specific toxicity to the reproductive system of males cannot be excluded.</p> | | | | |
| 3. In the available developmental study an increase in resorptions and a decrease in litter | | | | |

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size were observed at a dose level also inducing maternal toxicity. The level of detail on this study is not sufficient to allow an assessment whether the increase in resorptions are secondary to the maternal toxicity. A reduction in maternal body weight, especially at the latter stages of gestation, could also be secondary to the resorptions. Please provide additional information on this study including net weight gain of the dams (excluding uterus + contents). Additionally, the data of the two-generation study of Edwards (2010) (given for combined generations in this proposal, but given per generation in the Proposal for Harmonised Classification and Labelling of Phenol, dodecyl, branched from SI-Group UK, Ltd, 10 October 2012) show that reductions in pup weight in the F1 rats occur at 15 mg/kg bw/d, which is also a developmental toxicity effect. Therefore, please consider this effect and provide a justification for classifying or not for developmental toxicity.

4. We do not agree with the determination of the SCL (p. 114-118 of the proposal). We suggest to follow the method as described in the Guidance on the Application of CLP criteria (v 3.0, November 2012, http://echa.europa.eu/documents/10162/13562/clp_en.pdf). Summarized, the ED10 (the dose corresponding with a 10% change in response compared to the background response) must be derived by linear extrapolation or by using Benchmark dose software. Based on the ED10 the substance must be placed in a potency group considering potential modifying factors (see Table 3.7.2.5.5 in the guidance document) and the corresponding SCL can then be assigned. The proposed SCL of 1.5% differs significantly from the SCL of either 0.03% or 0.3% that are expected from the provided data, based on the guidance document. A new SCL proposal, following the steps in the guidance document, is therefore essential.

Specific comments:

- a. The calculation method using $NOAEL / 1000 * 100\%$ is not a correct method for the derivation of an SCL because this is based on a limit dose of 1000 mg/kg bw/day. However, as described in paragraph 3.7.2.5.7 of the guideline, there is no agreement on a specific dose as a limit dose. Therefore, the ED10 must be taken as a basis, according to the guidance. We are happy that the ED10 was derived by BMD software, as we feel this is the better of the two options given in the guidance for deriving the ED10.
- b. The ovary weights were identified as the most consistent and sensitive alteration for the reproductive effects (p 114). However, we do not agree that the male fertility endpoints should not be not considered (see above). Thus, please provide an explanation why ovary weight was chosen as the critical endpoint.
- c. In the proposal, "a benchmark response (BMR) of one standard deviation below the control mean value was selected, as this adequately represents the risk of approximately 10% of a population exhibiting a detectable change in a continuous endpoint (Crump, 1995)". Crump (1995) indeed states that the level of one standard deviation from control values are similar to a 10% effect level. However, this might hold for epidemiological studies, with a human population containing natural variation. For the animal studies considered in the present case, this similarity does not hold, as explained by Slob (2002): "Some authors have proposed to define effect sizes relative to the "natural" variation [in other words: the standard deviation] in the controls (Crump 1995; Gaylor and Slikker 1990). However, in a typical toxicity study (using inbred animals) the variation in the observations mainly reflects the heterogeneity in the experimental conditions. Normally we try to minimize the experimental variation in toxicity studies, and the "natural" variation that we observe in any such study quantifies the extent to which we did not succeed in that. Clearly, this is not natural variation in any biological sense, and therefore it cannot serve as a standard in defining the benchmark response". Therefore, it is our opinion that the BMR of one standard deviation below the control mean value does not represent a 10% effect level below the background in this case and cannot be used as ED10 value for deriving an SCL. It

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is proposed to calculate the 10% effect level by applying linear extrapolation or by using benchmark dose software according to the guidance. Further, the lowest of the calculated lower 95%-confidence limits of the ED10 was taken to derive an SCL, while according to the guidance the ED10 itself must be used.

d. The potency banding as proposed in the ECHA guidance was considered unnecessary by the authors, as the SCL was validated to existing data of substances containing TPP. However, NOAELs and LOAELs were used for this validation, without any information on the corresponding effect levels. On average, NOAELs correspond to an effect level of 5% when based on continuous data. Individual NOAELs may correspond to notably higher (or lower) than 5% effect levels (Bokkers and Slob (2007) and Kavlock et al. (1995) as cited in the EFSA BMD guidance document (2009)). The validation with existing data is therefore not sufficient to conclude on the adequacy of the SCL.

References

Bokkers, B.G.H. and Slob W. (2007). Deriving a data-based interspecies assessment factor using the NOAEL and the Benchmark dose approach. Crit. Rev. Toxicol. 37: 353-377.

Crump, K.S. (1995) Calculation of benchmark doses from continuous data. Risk Analysis 15(1), 79-89.

EFSA, 2009, Scientific Opinion: Use of the benchmark dose approach in risk assessment. Guidance of the Scientific Committee. The EFSA Journal (2009) 1150, 1-72.

Kavlock RJ, Allen BC, Faustman EM, Kimmel CA. (1995). Dose-response assessments for developmental toxicity IV. Benchmark doses for fetal weight changes. Fundam Appl Toxicol 26, 211-222.

Slob, W. (2002) Dose-response modeling of continuous endpoints. Tox. Sci. 66, 298-312.

Dossier Submitter's Response

Response to (1): We agree H360f should be changed to H360F.

Response to (2): We agree that changes to male reproductive organ weights cannot always be attributed to decreased body weight gain, but we disagree that this is sufficiently clear in the TPP data to attribute the effects solely as direct effects to the male system. One should consider the severity of the effect (both in degree and speed of occurrence), as well as the age of the animal at the onset of the effects to body weight (fully mature adult or pre-/ during sexual maturation). To illustrate the importance of these considerations, the tables below display body weight, organ weight, and relative organ weights and provide a comparison to information provided in OECD draft guidance 151. The systemic toxicity observed in male rats treated with 200 mg/kg/day, 36% decrement in body weight, far exceeds regulatory guidance for testing or interpretation of reproductive toxicity (target of approximately 10% effect of treatment upon body weight). The figures that follow the tables provide a visual representation of the relationship between body weight and prostate, testes, and ovary weights:

- (a) Ovary weight was unresponsive to changes in body weight due to feed restriction. In contrast, ovary weight decreased more sharply than body weight in the TPP studies.
- (b) Testicular weight was also relatively unresponsive to changes in body weight due to either feed restriction or TPP exposure. At the most severely affected body weights, testes weight decreased.
- (c) Parallel response slopes occurred for male body weight vs. male accessory organ weight (prostate) for the results of TPP data and feed restriction studies, suggesting

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that the interaction between body weight and organ weight were similar.

Shorter-duration dosing at very high exposure levels produced more severe effects upon the weights of the male reproductive organs than produced to body weight (n = 5/group). However, as the duration of exposure increased to seventeen weeks or longer, the effects to the male reproductive organs were generally commensurate with the degree of change to body weight (n = 30/group). Given that male reproductive effects have been associated with body weight decrements, we do not believe that the male data warrant an interpretation of "clear evidence" of reproductive toxicity, and we do not believe it is appropriate to propose a Repr. 2 for males in addition to the proposal for a Repr. 1B based upon data for the females. We concur with the Commenter that it is unclear if changes to the adrenal are related to hormone systems.

% Decrease in Body and Organ Weights (Compared to Control)

| Terminal Weight % | Two-Gen (F0) (15 mg/kg) | 90 Day (50 mg/kg) | Two-Gen (F0) (75 mg/kg) † | Two-Gen (F1) (75 mg/kg) † | One-Gen (F0) (125 mg/kg) † |
|--------------------|----------------------------|----------------------|------------------------------|------------------------------|-------------------------------|
| <u>Body Weight</u> | -1 | -12** | -19** | -28** | -26** |
| Testis | -3 | -3 | -8* (L) | -9** (R) | -5* (R) |
| Epididymides | +1 | -9 | -15** | -7** (R) | -17** |
| Prostate | -4 | -16 | -22** | -13* | -36** |
| Seminal Vesicles | -7 | -11 | -30** | -17** | -44** |

†highest dose tested

* = Significantly different from the control group at 0.05 using Dunnett's test

** = Significantly different from the control group at 0.01 using Dunnett's test

TPP Data includes 90-day (Haas, 2012), One-Gen (Knapp, 2006), and Two-Gen (Edwards, 2012) data.

(L) left; (R) right

% Decrease in Organ Weight (Relative to Body Weight)

| Terminal Weight % | Two-Gen (F0) (15 mg/kg) | 90 Day (50 mg/kg) | Two-Gen (F0) (75 mg/kg) † | Two-Gen (F1) (75 mg/kg) † | One-Gen (F0) (125 mg/kg) † |
|--------------------|----------------------------|----------------------|------------------------------|------------------------------|-------------------------------|
| <u>Body Weight</u> | -1 | -12** | -19** | -28** | -26** |
| Testis | -2 | +11 | +14** | +29** | +28** |
| Epididymides | +2 | +3.5 | +4 | +30** | -12** |
| Prostate | -3 | -4 | -4 | +20** | -13 |
| Seminal Vesicles | -6 | +1 | -14** | +16** | -25** |

†highest dose tested

* = Significantly different from the control group at 0.05 using Dunnett's test

** = Significantly different from the control group at 0.01 using Dunnett's test

% Decrease in Organ Weight (Relative to Brain Weight)

| Terminal Weight % | Two-Gen (F0) (15 mg/kg) | 90 Day (50 mg/kg) | Two-Gen (F0) (75 mg/kg) † | Two-Gen (F1) (75 mg/kg) † | One-Gen (F0) (125 mg/kg) † |
|-------------------|----------------------------|----------------------|------------------------------|------------------------------|-------------------------------|
| <u>Brain</u> | -1 | -0.5 | -1 | -5** | 0 |
| Testis | -2 | -2 | -7 | -4 | -5* (R) |
| Epididymides | 1 | -9 | -14** | -2 | -17** |
| Prostate | -3 | -16 | -21** | -9 | -36** |
| Seminal Vesicles | -6 | -11 | -29** | -13** | -44** |

†highest dose tested

* = Significantly different from the control group at 0.05 using Dunnett's test

** = Significantly different from the control group at 0.01 using Dunnett's test

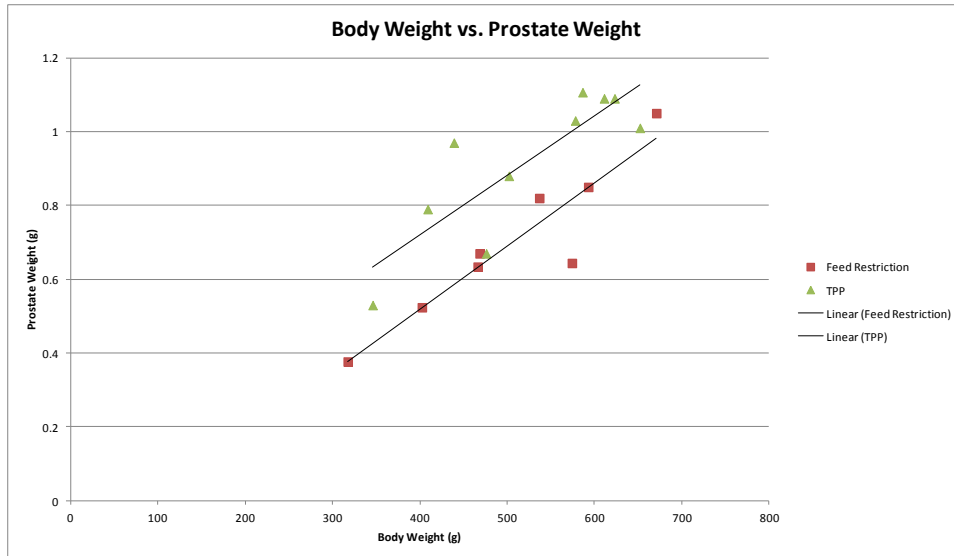
% Decrease in Organ Weight with % Decrease in Body Weights (Dietary Modulation)

| | 10% | 15% | 20% | 30% | 40% |
|--------------|--------------|----------------|--------------|----------------|----------------|
| Testis | -2 (-13.3-3) | 7 (2-11.9) | 3 (-0.3-4.9) | 0 (-15.4-13.2) | 6 (-10.8-24.3) |
| Epididymides | 3 (1.4-4.7) | 7 (3.2-10.8) | 6 (0.6-10.4) | 1 | 24 |
| Prostate | 13 (4.9-19) | 15 (12.6-17.3) | 12 (0-23.3) | 35 (18.6-53.9) | 34 (21.5-41.5) |

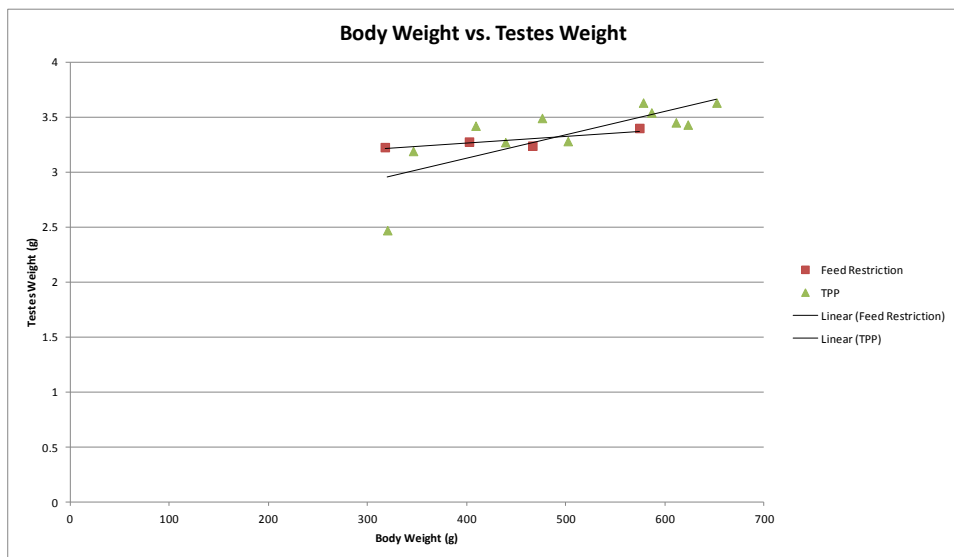
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Seminal Vesicles 12 (6.5-22.7) 16 (11.4-20.5) 23 (15.5-30.7) 24 44

Data from OECD Draft Guidance Document 151 in support of OECD Test Guideline 443 on an Extended One Generation Reproductive Toxicity Study. Version 3- April 2012. (last accessed May 17, 2013 http://www.oecd.org/env/ehs/testing/GD%20151_Oct%202012_clean2.pdf)

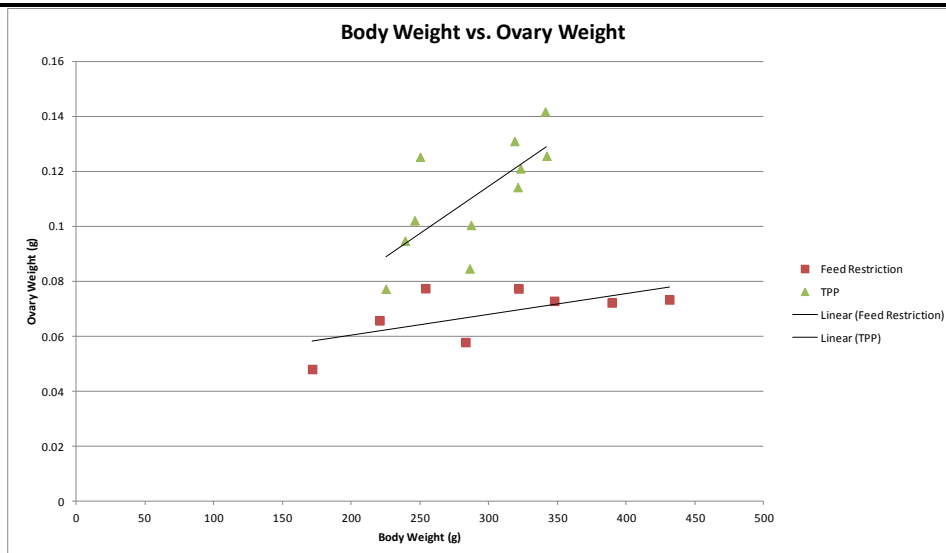


Feed Restriction Data (Chapin et al., 1993; Seki et al., 1997)
 TPP Data includes 90-day (Haas, 2012), One-Gen (Knapp, 2006), and Two-Gen (Edwards, 2012) F0 data.



Feed Restriction Data (Chapin et al., 1993)
 TPP Data includes 90-day (Haas, 2012), One-Gen (Knapp, 2006), and Two-Gen (Edwards, 2012) F0 data.

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Feed Restriction Data (Chapin et al., 1993; Seki et al., 1997)

TPP Data includes 90-day (Haas, 2012), One-Gen (Knapp, 2006), and Two-Gen (Edwards, 2012) F0 data.

Response to (3): The developmental toxicity report did not provide corrected (net) body weight changes. Maternal body weight was measured on gestation days 0, 6, 15, and at termination. The differences in body weight gain between gestation days 6 – 15 reflect both maternal and uterine weight changes:

Control: 50 g

20 mg/kg/day: 48 g

100 mg/kg/day: 50 g

300 mg/kg/day: 19 g (significantly different from control)

Please also note that the study originally included a group that was dosed at 500 mg/kg/day which was terminated due to excessive mortality (31%). Regarding pup weights in the two-generation rat reproduction study, please see the response to Comment 3, in which the values for the F1, F2, and F2a pup weights are provided. No effects upon pup weight were observed in the F2 or F2a litters at 15 mg/kg/day; mid-dose differences in the F1 pups were inconsistent and not considered an adverse finding by the study director.

Response to (4): 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.%.

Responses to specific comments:

(a)

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With regard to the limit dose as part of the basis for the SCL determination: OECD 416 test guideline indicates that 1000 mg/kg/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." (paragraph 16, OECD Test Guideline 416, adopted 22 January 2001; <http://www.oecd-ilibrary.org/docserver/download/9741601e.pdf?expires=1367794963&id=id&accname=guest&checksum=05A881A766A1858623A7713EAF98AD53>). Due to the physical chemical properties of TPP (high viscosity, very low volatility) and use (manufacturing intermediate for additive packages and engine oils), we have no reason to believe that human exposure would warrant a higher potential test dose than 1000 mg/kg/day. Skin contact is the most like route of human exposure; however, the test substance is a skin irritant and would present animal welfare concerns if tested for reproductive toxicity by this route. Recent dermal penetration test data have indicated that only approximately 3% of an applied dose is likely to be absorbed through the skin. Consequently, due to low dermal absorption and the absence of significant exposure by other routes, the limit dose of 1000 mg/kg/day was a reasonable maximum dose.

Exposure assessments conducted for the TPP Chemical Safety Report (CSR) further supports low exposure potential. The predicted dermal exposure to TPP for workers, determined using the ECETOC TRA tool (www.ecetoc.org), demonstrates that the exposure potential is well below the 1000 mg/kg/day limit dose. In addition, the exposure assessment found in the CSR of Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased (EC Number 272-234-3), a representative lubricating additive that contains TPP as an impurity, also demonstrates that the exposure potential to workers, professionals, and consumers is well below the 1000 mg/kg/day limit dose. Specifically, sections 10.1-10.6 of the CSR employ a tier 1 exposure assessment using the ECETOC TRA tool to predict dermal exposure to workers and professional users; appendix 4 of the CSR provides detailed calculations on how the modified (e.g., with exposure controls) exposure estimates were obtained. Sections 10.7 and 10.8 of the CSR use ConsExpo (v 4.1) to predict dermal and oral consumer exposures. As an example, the maximum predicted dermal exposure to the additive Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased, after applying modifying factors (from the CEFIC CSA tool with ATIEL-ATC use groups, v1.0), is 1.1 mg/kg/day. To calculate the amount of TPP exposure from this representative lubricating additive, the amount of residual TPP (6.7%) and the expected dermal absorption of TPP (3%) must be factored in and results in 0.002 mg/kg/day TPP (1.1 mg/kg/day * 6.7% * 3.0%). This is 750-fold lower than the NOAEL (15 mg/kg/day TPP) used to establish an SCL used for self-classification. This demonstrates that the exposure potential is extremely low, and thus, the test guideline limit dose of 1000 mg/kg/day is sufficient for testing and classification.

(b)

Please see comments above regarding male reproductive organs. Data for the males failed to meet the criteria for clear evidence of reproductive effects. Ovary weight was selected for the reasons stated earlier: it was the most sensitive reproductive parameter consistently affected in the TPP studies and did not appear to be secondary to general health effects (in our opinion and the opinion of the study directors responsible for study interpretation).

(c)

Thank you for your comment. We believe that the benchmark dose modeling approach using a BMR of one standard deviation is appropriate since the toxicity studies conducted with TPP were performed on Sprague-Dawley rats as the test species. The Sprague-Dawley is an outbred rat strain and biological variability is intentional. However in response to the commenter, we derived the ED₁₀ values using a 10% effect level by applying linear

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extrapolation as described by the ECHA guidance (Guidance on the Application of the CLP Criteria, Version 3.0, November 2012, Section 3.7.2.5.3.3) for continuous or parametric data. The estimated ED₁₀ values from all three studies are still greater than 15 mg/kg/day. The ED₁₀ estimations for each study are presented in the chart below.

Estimation of ED₁₀ values using linear extrapolation for ovary weight in rats exposed to TPP

| 1 - Generation Study F0 Females Ovary and Oviduct Weight (Knapp, 2006) | | | | | | |
|---|----|----------|--------------------|----------------------|---------------|------------------------------|
| Dose (mg/kg/day) | N | Mean (g) | 90% of Control (g) | Calculation of Slope | Interpolation | ED ₁₀ (mg/kg/day) |
| 0 | 30 | 0.144 | 0.1296 | 1250 | 0.0124 | 20.5 |
| 5 | 30 | 0.142 | | | | |
| 25 | 29 | 0.126 | | | | |
| 125 | 30 | 0.1 | | | | |

| 2 - Generation Study F0 Females Ovary Weight (Edwards, 2012) | | | | | | |
|---|----|----------|--------------------|----------------------|---------------|------------------------------|
| Dose (mg/kg/day) | N | Mean (g) | 90% of Control (g) | Calculation of Slope | Interpolation | ED ₁₀ (mg/kg/day) |
| 0 | 30 | 0.12 | 0.108 | 2041 | 0.006 | 27.2 |
| 1.5 | 29 | 0.121 | | | | |
| 15 | 30 | 0.114 | | | | |
| 75 | 29 | 0.0846 | | | | |

| 2 - Generation Study F1 Females Ovary Weight (Edwards, 2012) | | | | | | |
|---|----|----------|--------------------|----------------------|---------------|------------------------------|
| Dose (mg/kg/day) | N | Mean (g) | 90% of Control (g) | Calculation of Slope | Interpolation | ED ₁₀ (mg/kg/day) |
| 0 | 30 | 0.105 | 0.0945 | 1583 | 0.0085 | 28.5 |
| 1.5 | 30 | 0.0993 | | | | |
| 15 | 30 | 0.103 | | | | |
| 75 | 27 | 0.0651 | | | | |

(d)

The original determination of the SCL was based upon the NOAEL values determined in the reproduction studies. However, upon publication of the application guidance criteria, ED₁₀ values and their confidence limits were determined utilizing the BMD software. As noted by the commenter, continuous data, such as ovary weight, typically has a detection level of approximately 5% difference from control in well-conducted studies. We utilized a lower confidence limit rather than the ED₁₀ itself to incorporate data variability. Validation with existing data is preferable to selection of a default method absent of a clear scientific reasoning.

RAC's response

1. Thank you for the support for classification as Repr.1B, H360F
2. The reduced epididymal sperm count in animals has been used as justification of the classification so your view was at least in part shared by RAC.
3. The developmental toxicity has been considered; however, the maternal toxicity seen was considered as being greater than the observed fetal toxicity. Therefore the existing data do not warrant classification of TPP as a developmental toxicant.

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4. The calculations of the concentration limits in the RAC opinion are based on based on the new Guidance on the application of the CLP criteria (Version 4.0 – November 2013, section 3.7.2.5. Setting of specific concentration limits). For medium potency substances, such as TPP, the GCL should be used, namely 0.3 % for substances classified as Repr. 1B according to the CLP Regulation.

| Date | Country | Organisation | Type of Organisation | Comment number |
|------------------------------|---------|--------------|----------------------|----------------|
| 15.04.2013 | Denmark | | MemberState | 10 |
| Comment received | | | | |
| Agree. | | | | |
| Dossier Submitter's Response | | | | |
| Thank you for your comment. | | | | |
| RAC's response | | | | |
| Thank you for your view. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---------|--------------|----------------------|----------------|
| 18.04.2013 | Germany | | MemberState | 11 |
| Comment received | | | | |
| <p>p.53 (Edwards et al, 2012) Please add a justification why pup effects at 15 mg/kg bw/d (dose without maternal toxicity) are considered as not relevant for classification for developmental effects. The implementation of the precise data of table 40 from the previous dossier (p. 78) would facilitate to evaluate data and to decide on an appropriate classification. Add this fact to a further discussion why classification in reprotoxic category 2 is not appropriate for the substance. If this effect will be relevant for classification, this would influence the derived SCL.</p> <p>p.63 It should be discussed why the classification as reprotoxic category 2 is not appropriate for the substance. Please add the discussion on relevant arguments and why it is not justified to classify the substance. Explain how severe the maternal toxicity is. Indicate, which dams were affected by the body weight changes to which degree and how this effected the pups. Also add the data from the withdrawn Table 46 and Table 47 from the previous dossier (p.87/88). Compare the seen malformations to the classification criteria. To facilitate the further evaluation indicate the percentages of spontaneous incidences of the observed malformations in your laboratory control animals, thereby covering a sufficient time scale. Please add also the corrected body weight by subtraction of the uterus weight from the body weight of the dams, especially in the high dose group (75 mg/kg/day). This is important for judging whether the body weight reduction of the dams is severe, because the decreased litter size in the high dose group could lead to and explain the decreased body weight in the dams.</p> <p>p.71 and p.73 (Knapp, 2009a,b) High mortality was seen at doses of 800 mg/kg/day. This effect could be relevant for classification as acute toxic category 4, if it occurs within 48 hours after administration. Please add a justification why classification as acute toxic category 4 may or may not appropriate.</p> <p>p. 84 A study from Haas, 2010, is reported, but the evaluation is missing in the dossier. Please add the evaluation.</p> | | | | |

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p.89 The notes for F1 females treated with 1000 mg/kg/day and 300 mg/kg/day are the same. Be so kind to check if this is correct.

p. 118 Please add the results of the study conducted by Knapp et al., 2008, to the list.

Dossier Submitter's Response

- With regard to p. 53/pup weight: Please see the data provided for Comment 3. Pup weight was not affected in the F2 or F2a pups. Differences were inconsistently observed in the F1 pups. In contrast, effects upon pup weight at 75 mg/kg/day were observed consistently and indicate that both generations were similarly responsive. The data do not support classification for developmental effects.
- With regard to p. 63/selection of reproductive toxicity classification (development): The effects at 300 mg/kg/day in the OECD 414 study occurred in the presence of significant maternal toxicity.
- With regard to p. 71-73, high mortality: The TPP dossier provides acute toxicity data obtained by acute toxicity test guideline methods. The TPP classification for acute toxicity is based upon this data. Mortality occurred in the Knapp 2009a,b studies following 1 – 4 days of dosing.
- With regard to p. 84/Hass 2010 study: The information for Haas 2010 is provided:



Haas, 2010

- With regard to p. 89/notes for F1 females at 1000 and 300 mg/kg/day: The corrections are as follows:

Pg 88: Please note correction (underlined)

**NOTE: Identified organ weight changes relative to body weight corresponded to significantly reduced final body weight compared to controls.*

F₁ male 1000 mg/kg/day final body weight – 496 ± 47.3, ~ -21% vs. control

F₁ male 300 mg/kg/day final body weight – 550 ± 66.4, ~ -12% vs. control

F₁ male control group final body weight – 627 ± 65.7

Pg 89: Please note correction (underlined)

F1 females treated at 1000 mg/kg/day (67 mg/kg/day TPP):

**NOTE: Identified organ weight changes relative to body weight corresponded to significantly reduced final body weight compared to controls.*

F1-main female final body weight – 292 ± 32.0, ~ -8% vs. control

F1-main female control group final body weight – 316 ± 24.3

F1 females treated at 300 mg/kg/day (20.1 mg/kg/day TPP)

**NOTE: Identified organ weight changes relative to body weight corresponded to significantly reduced final body weight compared to controls.*

F1-main female final body weight – 307 ± 27.7, ~ -3% vs. control

F1-main female control group final body weight – 316 ± 24.3

- With regard to p. 118/please add Knapp et al., 2008 to the list: This study appears as (iv) in page 118.

RAC's response

Thank you for your comment. The additional data provided were used in the RAC conclusion.

Please see the final justification for classification as Repr.1B in the opinion.

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| Date | Country | Organisation | Type of Organisation | Comment number |
|--|----------------|--------------|-------------------------|----------------|
| 19.04.2013 | United Kingdom | | Company-Downstream user | 12 |
| Comment received | | | | |
| <p>Whilst effects on fertility have been demonstrated in a one-generation study there is no clear evidence of specific reproductive toxicity in the absence of other toxic effects. Since no treatment related adverse effects on reproductive parameters could be determined at dose levels that did not elicit general systemic toxicity in both the one generation and definitive two generation study, we support the previous dossier classification as Category 2 Reproductive effects (adverse effects on sexual function and fertility).</p> | | | | |
| Dossier Submitter's Response | | | | |
| <p>Thank you for your comment. Although reproductive effects occurred only at dose levels that also produced systemic health effects, the health effects were of insufficient magnitude in females to interpret reproductive effects as secondary to other health manifestations.</p> | | | | |
| RAC's response | | | | |
| <p>The option of classification of TPP to Repr. Cat 2. has been considered by RAC as proposed. However, as explained in the Opinion Development Document, a justification Repr. 1 was found more appropriate.</p> | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|--|---------|--------------|----------------------|----------------|
| 18.04.2013 | France | | MemberState | 13 |
| Comment received | | | | |
| <p>P.33: In the study of Haas et al. (2012), we observe reduced body weight and body weight gain at all doses. We consider that the NOAEL for general toxicity is 50 mg/kg/day and the LOAEL is 100 mg/kg/day. Thus, in repeated dose toxicity studies, the effects are observed between 100 and 180 mg/kg. However, there is no impact on the classification for repeated toxicity according to the CLP.</p> <p>p.78-80 Two new studies (Thomas et al., 2012a et 2012b) added in this CLH report comfort us for the classification in Repr 1B, for fertility.</p> | | | | |
| Dossier Submitter's Response | | | | |
| <p>With regard to classification for repeated exposure: In our opinion, the effects observed did not warrant classification for repeated toxicity.</p> | | | | |
| RAC's response | | | | |
| <p>Your support for classification as Repr. 1B has been noted. STOT RE classification was not proposed by the Dossier submitter and it was not considered by RAC.</p> | | | | |

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

| Date | Country | Organisation | Type of Organisation | Comment number |
|--|---------|--------------|----------------------|----------------|
| 18.04.2013 | Germany | | MemberState | 14 |
| Comment received | | | | |
| <p>p.35 (Haas, 2012) More data on severity or amount of reduction are needed for the anaemic effects and liver cell vacuolation that were observed in the 90-day study.</p> <p>p. 40 (Harriman, 2004) Anaemic effects at doses relevant for classification are reported.</p> | | | | |

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The level of reduction should be given for relevant parameters to allow decision on STOT RE.

Liver cell vacuolation is an adverse effect that may be relevant for classification at the doses observed (≥ 180 mg/kg bw/d, 28-day study).

Severity scores should be added to allow conclusion on the necessity of classification.

p.42 (Reyna and Thake, 1988) Be informed that the values on decreased body weight gain of the 2500 ppm group are missing.

In the old dossier table 28 (p. 61) reports bone marrow hyperplasia at 300 mg/kg bw/d. This effect may be a serious effect at the guidance value for classification with STOT RE. The information lacks in the updated dossier. Effects on haematology parameters should be reported, if available (or whether examined).

p. 46 Systemic or organ-specific toxic effects occurring at oral doses up to 300 mg/kg bw/d in a 28 day study may be relevant for classification (see Table 3.9.2.2. Guidance to CLP regulation). Please compare in addition to the results of the 90-day study the observed non-specific and organ-specific effects of the 28-day study with the CLP guidance values.

Dossier Submitter's Response

Response to the comment regarding p.35 (Haas, 2012) "More data on severity or amount of reduction are needed for the anaemic effects and liver cell vacuolation that were observed in the 90-day study":

Data tables are provided below. It is apparent that effects occurred at dose levels with significant systemic health effects; the data do not warrant classification for repeated-exposure target organ effects.

Table 1. Summary of Hematology Values (90-Day Study - Haas, 2012)

| Dosage (mg/kg/day) | Males | | | | | Females | | | | |
|------------------------|-------|------|------|------|--------|---------|------|------|------|--------|
| | 0 | 50 | 100 | 150 | 200 | 0 | 50 | 100 | 150 | 200 |
| White Cells (thous/uL) | 7.78 | 7.60 | 7.43 | 7.08 | 5.55 | 6.01 | 5.55 | 5.15 | 5.57 | 3.51** |
| Red Cells (mil/uL) | 9.15 | 8.95 | 8.84 | 8.69 | 8.41** | 8.32 | 8.52 | 8.34 | 8.04 | 8.21 |
| Hemoglobin (g/dL) | 16.7 | 16.5 | 16.5 | 16.6 | 15.8* | 16.2 | 16.1 | 15.7 | 15.4 | 15.5 |
| Hematocrit (%) | 45.7 | 44.8 | 45.1 | 45.0 | 42.7 | 43.7 | 43.8 | 41.9 | 41.6 | 42.0 |
| MCV (fL) | 49.9 | 50.1 | 51.0 | 51.8 | 50.7 | 52.5 | 51.5 | 50.3 | 51.8 | 51.2 |

* = Significantly different from the control group at 0.05 Dunnett's test

** = Significantly different from the control group at 0.01 Dunnett's test

Table 2. Incidence Liver Cell Vacuolation (90-Day Study - Haas, 2012)

| Dosage (mg/kg/day) | Males | | | | | Females | | | | |
|---|-------|----|-----|-----|-----|---------|----|-----|-----|-----|
| | 0 | 50 | 100 | 150 | 200 | 0 | 50 | 100 | 150 | 200 |
| Liver* | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Vacuolation, hepatocellular, periportal | 0 | 0 | 0 | 3 | 5 | 0 | 0 | 0 | 3 | 4 |

* = Number of tissues examined from group.

Response to the comment regarding p. 40 (Harriman, 2004) "Anaemic effects at doses relevant for classification are reported. The level of reduction should be given for relevant parameters to allow decision on STOT RE. Liver cell vacuolation is an adverse effect that

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may be relevant for classification at the doses observed (≥ 180 mg/kg bw/d, 28-day study). Severity scores should be added to allow conclusion on the necessity of classification."

The data tables are provided below for hematology and liver cell vacuolation. Effects to hematology parameters and liver occurred only at ≥ 180 mg/kg/day, above the classification criteria. The report provided the following description for histopathological findings in the liver:

"In the liver, minimal to mild centrilobular hepatocellular hypertrophy was noted in the 60, 180 and 300 mg/kg/day group males and the 180 and 300 mg/kg/day group females. The severity and/or incidence of this change tended to increase with dose, with all males and females in the 300 mg/kg/day group affected at the primary necropsy. Hepatocellular vacuolization, consistent with fatty change, was noted in 3/5 males and 1/5 females in the 300 mg/kg/day group. The vacuolization tended to be at the periphery of the hypertrophied hepatocytes and extended to the periportal regions. Both of these changes contributed to the higher liver weights."

Summary of Hematology Values (28-Day Study - Harriman, 2004)

| Dosage (mg/kg/day) | Males | | | | Females | | | |
|------------------------|-----------|------|------|-----------|-----------|------|--------|--------------|
| | 0 | 60 | 180 | 300 | 0 | 60 | 180 | 300 |
| White Cells (thous/uL) | 8.9/11.4 | 9.1 | 7.9 | 8.2/13.6 | 6.3/9.0 | 6.8 | 7.1 | 5.3/8.8 |
| Red Cells (mil/uL) | 8.06/8.84 | 8.01 | 7.65 | 7.66/8.11 | 8.09/8.35 | 7.78 | 7.43 | 7.24/7.97 |
| Hemoglobin (g/dL) | 14.8/16.1 | 15.2 | 14.2 | 14.3/15.7 | 15.3/15.8 | 14.9 | 14.0** | 13.5**/15.2 |
| Hematocrit (%) | 42.1/45.7 | 42.8 | 39.8 | 40.0/43.7 | 42.7/43.7 | 41.8 | 39.0** | 38.22**/42.3 |
| MCV (fL) | 52.2/51.7 | 53.5 | 52.1 | 52.2/54.1 | 52.8/52.3 | 53.8 | 52.5 | 52.9/53.1 |

Week 4(0 – 300 mg/kg/day)/Week 6(0 and 300 mg/kg/day)

** = Significantly different from the control group at 0.01 Dunnett's test

Incidence of Liver Cell Vacuolation (28-Day Study - Harriman, 2004)

| Dosage (mg/kg/day) | Males | | | | Females | | | |
|---|-------|----|-----|-------------------------|---------|----|-----|-------------|
| | 0 | 60 | 180 | 300 | 0 | 60 | 180 | 300 |
| Liver* | 10 | 5 | 5 | 10 | 10 | 5 | 5 | 10 |
| Vacuolation, hepatocellular, periportal | 0 | 0 | 0 | 3 (minimal to moderate) | 0 | 0 | 0 | 1 (minimal) |

Week 4(0 – 300 mg/kg/day)/Week 6(0 and 300 mg/kg/day)

* = Number of tissues examined from group.

** = Significantly different from the control group at 0.01 Dunnett's test

Response to comment about p.42 (Reyna and Thake, 1988) "Be informed that the values on decreased body weight gain of the 2500 ppm group are missing."

The values on decreased body weight gain of the 2500 ppm were included in the robust study summary on pg. 42. Another way to look at the decreases in body weight for the 2500 and 5000 ppm group is shown below. Body weight gain was observed with the control and 2500 ppm group, however, there was a marked body weight loss at the 5000 ppm group, as compared to control.

Dose Dependent Decreases in Body Weight Gain (Reyna & Thake, 1988)

| Dose Group | Overall Cumulative Weight Gain (Mean) (g) | % Less Than Control (Cumulative) |
|------------|---|----------------------------------|
| Control | 115.2 | - |
| 2500 ppm | 40.9 | -64.5 |
| 5000 ppm | - 15.5 | -113.5 |

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Response to comment "In the old dossier table 28 (p. 61) reports bone marrow hyperplasia at 300 mg/kg bw/d. This effect may be a serious effect at the guidance value for classification with STOT RE. The information lacks in the updated dossier. Effects on haematology parameters should be reported, if available (or whether examined)."
The 28-day study (Harriman, 2004) did not identify a finding of bone marrow hyperplasia.

Response to comment "p. 46 Systemic or organ-specific toxic effects occurring at oral doses up to 300 mg/kg bw/d in a 28 day study may be relevant for classification (see Table 3.9.2.2. Guidance to CLP regulation). Please compare in addition to the results of the 90-day study the observed non-specific and organ-specific effects of the 28-day study with the CLP guidance values."

Effects occurred in the presence of significant systemic toxicity and above the thresholds for classification.

RAC's response

Thank you for your comment. The additional data provided were used in the RAC conclusion.

Please see the final justification for classification as Repr.1B in the opinion.

STOT RE classification was not proposed by the Dossier Submitter and it was not considered by RAC.

ATTACHMENT RECEIVED

1 **Comments on Annex XV dossiers proposing harmonised Classification & Labelling** (File name: COM_CLH_PC_Phenol Dodecyl Branched_SE), submitted on 19/04/2013 by Sweden (*ECHA note: This attachment has been copied under the section Toxicity to Reproduction*)