Peer Review of MRLs for TCP
(Tricresyl phosphate)

Reviewer #1

2-New TCP MRLs

1. Are the discussions of all MRLs logical and clear?

The inability to derive an acute oral MRL using animal and human data is clearly stated due to insufficient data. The discussions for derivation of oral MRL are appropriate for the intermediate-duration and chronic exposures. The discussions were logical and clearly stated.

2. Are the study and endpoint selection appropriate?

The derivation of the intermediate- and chronic-duration endpoint selections based on the available scientific data using adrenal cortex cytoplasmic vacuolization appears to be the most reliable, sensitive biomarker is appropriate. However, the use of ovarian interstitial cell hyperplasia (ovarian lesions) is questionable. If one examines the data closely (see Table 12 page 433 of NTP TR document, the ovarian lesions are described as minimal in grade severity. Although 6 out of 10 rats showed this effect at 3 months at 6mg/kg or 150 ppm TCP, it is noteworthy that ONLY 1 rats showed this effect at 9 months and NO rats displayed this effect at 2 years. Hence using ovarian lesions at 3 months this constitutes a LOAEL but this becomes a NOAEL at 9-24 months. The fact that this effect is at best minimal and disappears questions the use of this parameter as an adverse effect or merely an adaptive change that disappears with continued chemical exposure. Clearly the TCP induced alterations in adrenal cortex in rat and liver in mouse are adverse and need to be considered as the most sensitive endpoint for both

intermediate- and chronic-duration MRL derivation.. The use of ovarian lesions as sensitive endpoints is highly questionable due to both severity and reversibility.

3. Is the application of the PBPK model appropriate?

There use of PBPK models used to predict the point of departure for adrenal cortex lesions for the intermediate-duration MRL was appropriate. The use of PBPK models used to predict point of departure for chronic duration for adrenal cortex in female rat as well as hepatic lesions in male mouse was appropriate. Based upon the minimal severity of the ovarian lesion at 3 months and absence of this effect at 9-24 months, the use of PBPK to predict point of departure using the endpoint of ovarian lesions was not justifiable for both intermediate- and chronic-duration MRL.

4. Are you aware of other studies that would impact the MRLs?

I am not aware of any other studies that would impact the MRLs.

5. Do you concur with the MRLs as derived?

The use of ovarian lesions as a sensitive endpoint to derive intermediate- or chronic-duration MRL was not justifiable due to absence of effect after 3 months as well as the severity being minimal, suggesting that this might not constitute an adverse effect. The use of endpoints of adrenal lesions in female rats or liver lesions in mouse provides a more reliable, sensitive index of adverse effects produced by TCP.

In the charge to the peer reviewers in the Summary of two new MRLs for TCP, please note that it is a “Fischer 344 rat” and NOT Fisher.

3-REVISED MRLs

1. Are the discussions of the four revised MRLs still logical and clear?

The discussions for the four revised MRLs were easy to follow and clearly enunciated.

2. Do you concur with the four revised MRLs as derived?

With respect to TCEP, derivation of a revised MRL using renal tubule hyperplasia as a sensitive endpoint in female F344 for chronic-duration oral exposure was appropriate. In the case of TnBP, derivation of an intermediate-as well as chronic- duration oral exposure using urinary bladder hyperplasia in male rats as the most sensitive endpoint from the 10 week Arnold et al (1997) study for intermediate and the Auletta et al (1998a) 2 year dosing study for chronic were justifiable. With respect to TBEP, derivation of a revised intermediate oral exposure MRL using hepatocyte vacuolization in an 18-week dietary study was appropriate as an endpoint despite the fact that this hepatic change may represent an adaptive rather than adverse effect. The observed hepatic alteration is reflective of a change; however, at present time this alteration can not be explained, which does not diminish the fact that a change has occurred.

The following need to be addressed in the text:

1) Page 2 lines 2 & 4 change to "Fischer 344 rats"
2) Page 8 line 12 change to "…(0, 200 or 333 mg/kg day for 18 weeks)"
3) Page 18 lin6 text change to " …20/gender/group.."
4) Page 19 line 18 change to "….and not necessarily…"
5) Page 31 line 4 change to "…mice per gender per dose…'

Phosphate Ester Flame Retardants PEFR
Review of TCP (two new MRLs) and revised four of the previous nine MRLs

Reviewer #2

A. Two New MRLs for TCP (Intermediate-Duration and Chronic Duration Exposure)
1 – Are the discussions of the new MRLs logical and clear?

The discussion of the two new MRLs is somewhat confusing and unclear. The major source for the confusion is that the principal study is not discussed in the text for either MRL. Hence the experimental design, including the dose levels and the result for adrenal and ovarian lesions in female rats on which the NOAEL, LOAEL and $BMDL_{10}$ are derived are not given in the text of both the intermediate- and chronic-duration but only presented in Tables 28 and 34 at the very end of the discussion. Thus, it is not possible while reading the text to determine that these lesions in female rats as stated in the text were the most sensitive to TCP. For example, when female rats are said to be more sensitive than male rats and the dose levels and results for the males are given those of the female rat are not. Thus, there were no data from the female rats for comparison to the males and to demonstrate that females are more sensitive. The same is true for the 600 ppm TCP dose in males that resulted in a 100% incidence of male rats with adrenal lesion. Without the dose levels and incidence in female rats it was not possible to determine whether they too had an incidence of a 100%.

The document would be more logical and clear if the study used to determine the $BMDL_{10}$ is presented first. This should include the experimental design, including the dose levels and time pints, the results (including Tables 28 and 34), and then the conclusions including the NOAEL and LOAEL of the study. Other studies could then be presented and their results compared to the principal study used to calculate the $BMDL_{10}$. The text could then concluded by restating the selected study and its NOAEL and LOAEL and reference the already presented table containing the results used to calculate the $BMDL_{10}$.

The Tables 28 and 34 could indicate which results are statistically significant from the Controls. The footnote to the table should include the name of the statistical test and the p-value.

Since TCP is a mixture of isomers, it would be very useful to include in both the Rationale Statement and the Worksheets the purity and isomer composition of the TCP used in the NTP studies, since this study is the basis for both intermediate and chronic MLRs. It should identity of the other 21% component of the TCP solution used by NTP that was not TCP, i.e., dicresyl phosphates. It should also describe 75% of the TCP in the solution that could not be identified as specific TCP, i.e., as described by NTP as "Two peaks representing 24% and 30% ……. were identified as TCP esters whose isomeric composition could not be confirmed."

The following contains my specific comments of the **Selected MRL Rationale Statements**:

Page 24, First Paragraph, Lines 5-6: This sentence needs to be changed. The statement about the uncertainty of their examination is wrong. NTP clearly states what was examined microscopically and this does not include the ovaries and adrenal gland. Hence, they were not examined by NTP.

Page 24, Second Paragraph, Line 8. The dose levels and results for the female rats could be given and discussed here. This would allow comparison to the adrenal results for male rats, as

well as the mice results that follows and would support the statement that the males are less sensitive.

Page 24, Second Paragraph, Lines 12-14. Something needs to be stated as to why the incidence was 100% for 600ppm TCP at 3-months but 0/10 (0%) at both 9 and 15 months. Thus it should state that exposure to 600ppm TCP ceased t 3-months. The document could also state that the TCP-induce adrenal lesions in rats appeared to be reversible. More discussion is given to the less important adrenal lesions in mice were a mechanism is proposed than in female rats which are more sensitive to lesions. Is this mechanism of TCP accelerating spontaneous adrenal lesions also applicable to rats? The document only states it is applicable to mice. Why not also rats and if not why not and what then is the mechanism in rats. Something should be said about the mechanism in rats since it is proposed for mice.

Page 24, Second Paragraph, Lines 17-18. This sentence wrongly states that Latendresse used a considerably higher dose level when in fact Latendresse used only the second highest dose level of the NTP study in order to evaluated in greater depth the toxicity and mechanism of TCP.

Page 24, Second Paragraph, Line 24. The adrenal lesions in the mice should be identified as ceroid pigmentation since they are different from the female rats.

Page 24, last two Lines. The 3-months adrenal results for mice should be given before the 9, 15 and 24 months. This would better demonstrate that TCP might accelerate the occurrence of the lesions.

Page 25, Line 3 Add “female”, i.e., lesions in “female” rats.

Table 28. This table should include the 600ppm data at 3-months. If this data is not used to calculate the $BMDL_{10,}$ then the document should state why it was not used.

Page 31. Again the dose levels for female and male rats and mice should be given, i.e., on line 5 of this page.

Page 31, Line 8. Table 34 should be reference and the results discussed here before presenting the values for the LOAEL and NOAEL, since the results in Table 34 were used to derive the LOAEL and NOAEL. Furthermore the results presented in Table 34 are discussed in general term, while the actual data is not given in the text. It is not until the end of the text that the data is given by reference to Table 34. It would be better to send the reader to Table 34 at this point and to include the actual data in the text. The document can then continue with “Results of the 15-month…provided adequate data….for deviation of a chronic……MRL for TCP.”

The following contains my specific comments of the **Worksheets**:

Page A-48, Line 18. The 600ppm dose and its mg/kg-day should be included. Then on line 20, it should state why the 600ppm dose group was changed to control diet and that only the 3-month sacrifice supplied useable data to determine the NOAEL and LOAEL.

Page A-48, Lines 43-44. Should state or indicate the dose levels for the series of incidence. It is very confusing as to why there are five incidence at 3–months and only four incidences at 9-months, as well only four incidences for the ovaries on line 47. I assume the fifth incidence is for the 600ppm, although never stated in the text. It should be stated why the incidence of adrenal lesions were not elevated beyond 3-month in the highest (600ppm) dose group. It should also state why the 600 ppm dose group is not included in Table A-23. Was there something wrong with the data?

Page A-48, Line 48. Same as above. Should also state why there is no 600ppm response at 3-months for the ovaries since there is data for adrenal gland.

Page A-54-55. Same as above with respect to the 600ppm dose and indicating the dose levels for the series of incidence.

Page A-56, Line 4. Should be "15-month and 2-year sacrifices" not "3- and 9-month".

The following contains my specific comments of the **Other Pages**:
Page 10, Line 26. To be specific, the document should give the duration of the study used for the intermediate exposure: "intermediate-duration (10 weeks)."

Page 53, Lines 1-4. This sentence is confusing since it appears but does not state that survival was reduced by both 1,450 and 2,900. To be more specific, it would be better to rewrite as: "Survival was significantly reduced by both 1,450 and 2,900 mg/kg but not by the high dose level of 5,800 mg/kg (no explanation provided)."

Page 139, Lines 18-21. The document needs to better characterize the composition of the TCP used by NTP, since their study is the basis for both intermediate and chronic MLRs. It should state the identity of the other 21% of the TCP that was not TCP, i.e., dicresyl phosphates as well as the other 75% of the TCP, i.e., TCP esters whose isomeric composition could not be confirmed.

Page 141, Lines 27-28. Please identify the dose ranges in the parentheses. I assume they are the high dose level and not as presented the dose-range for the study. Either give the dose-range for the studies or include it the parentheses "(high dose level:13-….)".

Page 147, Line 28. Change "food" to "diet."

Page 227, Line22. Delete "low-dose" since the dose levels where significant toxic effects were observed in the studies were only the high dose levels and these dose levels are not low relative to human exposure.

Page 233, Line Delete the editorial "wide-scope." What does it specifically means?

2 – Are the study and endpoint selection appropriate?

The study and endpoints are appropriate. NTP studies are state of the art and extremely well documented.

3 – Is the application of the PBPK model appropriate?

The models in the EPA BMDS (version 2.1.1.) are very appropriate.

4 – Are you aware of other studies that would impact the MRLs?

I am not aware of any other study that would impact the MRLs.

5 – Do you concur with the MRLs as derived?

I concur with the derived MRLs.

B. Revised MRLs

1 – Are the discussions of the four 'revised' MRLs still logical and clear?

The discussion of the four 'revised' MRLs is logical and clear. The following are specific comments for the revised MRLs.

TCEP-chronic-duration.

Page 2, Line 16 and Page A-8, Line 43. The individual animal data for all histopathologic evaluations and all noted lesions and are available online at http://ntp.niehs.nih.gov/index.cfm?objectid=0365F4C1-0844-AAEC-7D20338BCC0058CF. NTP always publishes individual data. Using this data, the incidence of animals with at least one brain lesion for the 0, 44 and 88mg/kg/day is 4/50(8%), 8/50(16%), and 37/50(74%), respectively. CDC might chose not to include all the lesions, such as some minor lesions, i.e., brain stem compression. In any case some of the lesions can be combined to calculate a BMDL10.

TnBP-intermediate-duration

Table 10 and Table A-7 under Arnold et al., it should be "Males" not "Incidence."

TnBP -chronic-duration

For consistency with the other calculations of MRLs, the "Fit" figures for the model used to calculate the $BMDL_{10}$ using the male and F_0 female data should be included to assure the reader that the chosen models fit the data and that the selected $BDML_{10}$ in Table A-9 and A-10 are greater than the one chosen for the intermediate exposure.

TBEP -intermediate-duration

Page 19, Line 8, and A-31, Line 39. States that "Histopathology was restricted to the liver of males. " This implies that histology was only performed on the liver of male rats and not female rats. Since histology was also performed on the liver of female rats it should be changed to "Histopathological lesions were restricted to the liver of male rats"

2 – Do you concur with the four revised MRLs as derived?

I concur with the four revised MRLs with the possible exception as stated above that the incidence of total or some subset of brain lesions might be more suited than cerebrum gliosis in female rats for deriving the $BDML_{10}$ and MRL of TCEP-chronic duration.

REVIEW:
ATSDR Toxicological Profile
for
Phosphate Ester Flame Retardants

March 2012

Reviewer #3

REVIEW SPECIFICS:

B. Charge to Peer Reviewers

Responses –

1. Are the discussions of the new MRLs logical and clear? YES
2. Are the study and endpoint selection appropriate? YES
3. Is the application of the PBPK model appropriate? YES
4. Are you aware of other studies that would impact the MRLs? NO
5. Do you concur with the MRLs as derived? YES

3. Revised MRLs

1. Are the discussions of the four 'revised' MRLs still logical and clear? YES
2. Do you concur with the four revised MRLs as derived? YES

General Recommendations:

1. Exchange euthanatize or kill for sacrifice throughout document.
   This is not a religious experience.

TCP DISCUSSIONS in 2012 Profile

Profile Section		Profile Page, Line – Comments
1.	1PHS	PP 1 -8 – overview of profile - Well written summary of issues related to phosphate ester flame retardants. No suggested upgrades.
2.1	Background	p9, all Adequate – no additions proposed.
2.2	Summary	p10 Lines 25-29 Good point about TOCP as contaminant.
2.3	MRLs	**Initial presentation of MRLs to focus on** (summarized below)

				(2009 => 2012) mg/kg/day
p21	TCEP	chronic	revised *	0.3 => 0.2
		Appears reasonable based upon renal lesions		

p24 TnBP intermediate revised * 0.02 => 0.08
Reasonable based upon urinary bladder hyperplasia
p26 TnBP chronic revised * 0.02 => 0.08
Reasonable based upon rat urinary bladder lesions as indicated in the report. Hyperplasia is not neoplasia but certainly in not normal.
p29 TBEP intermediate revised * 0.2 => 0.09
agree with the use of hepatocellular hypertrophy and vacuolization as significant change and thus an endpoint to be used for MRL.
(2012) mg/kg/day
p34 TCP intermediate new * * 0.04
Unfortunately, as with other phosphate esters there is limited data available. The data used is principally from the NTP Study and based upon ovarian and adrenal cortex results. Interestingly there is a gender difference in the rodent studies for adrenal lesions, whereas both genders were affected in mouse studies. Calculations reasonable.
p35 TCP chronic new * * 0.02
Reasonable based upon ovarian data available.
p 34, line 1 to p37, line 25 – specific discussion of TCP MRLs
Linelogistic model appears to be appropriately applied and useful to the interpretation.
The most difficult part of this assessment is the understanding of mechanism of action being attributed to TCP. Even though the commercial grade product is anticipated to have some TOCP, which has been implicated with altered cholesterol metabolism and as well as interactions with Vitamin E and selenium. The lack of identifying the mechanism of action for TCP on the ovary and adrenal add further to the confidence we have in these data sets. Also the numbers of animals tested at any one dose is minimal. The continuing difficulty with the interstitial ovarian cell hyperplasia is that such changes are seen principally in the 7 and 15 mg/kg/day and in the two year study not at 7 but only at 15 mg/kg/day. The significance to reproduction and cancer still need to be identified; however, this does appear to be a finding associated with TCP since controls did not express.
The adrenal and hepatic findings (vacuolizations/ lesions) are equally challenging because control also demonstrate the changes.
Well summarized.

3.0 Health Effects

3.2.1.1 p43, lines 15-26 High doses of TCP exposures via vapors did have findings among them lethality. <2000,000mg/m3; while 1 hr exposures in rats did not demonstrate substantial findings.

3.2.2.1 p52, lines 20-53
For TCP, certainly high oral dosing (17 -24.8 gm of TCP/KG led to GI irritation, diarrhea and visceral hemorrhage and

even death. Even though no histopath remarkable that survivors in 28 day study showed no compound related alterations in any organs examined when rats were given approx. 1 gm/Kg of TCP.

Table 3-6

pp106-131 LSEs for TCP – Table 3-6, Figure 3-6

Tabular form quite helpful especially laid out by species, study and dose. Developmental effects in three studies raise the question in rats about long term exposures a lower doses (124 -400 mg/kg/day affecting viability of pups and litter size. There is no apparent explanation for a mechanism of action for TCP.

p139, lines 10-21

Interestingly, the NTP study used a mixed isomer preparation 79% TCP, 21% TMCP, 4% TPCP, <0.1% TOCP. For this section respiratory effects were not really seen consistently.

p139, lines 13-28 acceptabe

p140, lines 20-27

No major GI actions except diarrhea. Could be do to the bulk given or the trace contaminate TOCP at 0.321 mg/kg/day or less.

p141, lines 19-28 No hematological effects.

p144, line 25 to p145, line 8 Hepatic effects not dramatic; however, LDLs increased in one study where measured.

p147, line 28 to p148, line 4 reasonable statements about renal evaluations. Little to report

p148, line 12 to p149, line 21

The reported endocrine findings with TCP offer a substantial challenge to understanding the potential site of action. Reported increased in LDLs with the liver and the adrenal lipidosis with repeated exposures to TCP. The accumulation of the lipids were proposed to be due to the inhibition of neutral cholesteryl hydrolase (nCEH),

The adrenal lipidosis is complemented in the ovary when treated with TCP where the Hypertrophy of ovarian interstitial cells is described by "the interstitial cells were enlarged by abundant foamy cytoplasm, apparently due to lipid accumulation." (NTP p38). This hypertrophy of adrenal cortex was noted in both rats and mice (both genders) in the NTP study. This current ATSDR document strikes the correct balance for both the adrenal and ovarian findings since proven mechanisms have not been documented. Certainly the control of cholesterol metabolism and steroidogenesis appear involved. Of special note though are the P450 metabolism of TCP to more reactive agents that

could play a role as well with the longer exposures at higher dosages especially using commercial grade product.

p151, lines 25-34 Reductions in body weight would certainly be expected with reductions in food consumption with the higher exposures to TCP. Section appropriate.

Table 2, continued… TCP 'Discussions' in 2012 Profile

p155, lines 1-19
Discussion of immunocompetence and thyroid \ function appears to adequately reflect the findings available.

p157, line 23 to p158, line 34
The discussion of TOCP is important and can apply more broadly than just for neurological findings especially since commercial grade TCP was used with known isomers as discussed earlier. Good to discuss reductions in ACH esterase levels in both rats and mice.

p161, line 1 to p162, line 32
Excellent description of the reproductive findings for males and females. For the male, the findings of reduced fertility and abnormal sperm / atrophy of seminiferous tubules is relevant. For the female, references to the NTP study should lead the reader to plates 4 and 6 demonstrating the interstitial cell hyperplasia. Again the finding is important to report. Its importance as an endpoint of toxicity is an open question since fertility in the females was noted. Is it precancerous is another issue which is unresolved since no cancer cells were detected. A two year study should be long enough to detect a tumor endpoint as has been noted for diethylstilbestrol in rodents. (Baggs et al, 1991)
R.B. Baggs, R.K. Miller, and C. Odoroff, Carcinogenicity of Diethylstilbestrol in the Wistar rat: Effect of Postnatal Oral Contraceptive Steroids, Canc. Res. 51:3311-3315, 1991.

p165, lines 17-30
The developmental findings of reduced litter size and increased incidence of dead pups was confirmed across species and in multiple studies. The reason for the demise of fetuses/pups is not clear. The survivors were of normal weight and land marks. The description appears appropriate in this section.

p168, lines 24-29
This is a very important finding of no specific tumors associated with TCP (commercial grade). I would suggest adding to this section for emphasis commercial grade, which

should trigger the reader to consider that TOCP and other congeners were present as well.

p169, lines 20-29

Lethal Exposures in Rabbits due to dermal exposures. Findings appear appropriately reported with LD50 reported at <20,000 mg TCP/KG.

p179, lines 26-28

Dermal exposures in humans and rabbits. Perhaps the addition should indicate that corrosion was not noted in a single study; however, other whole animal effects were noted: diarrhea and lethality (LD50 <20000 mg TCP/kg)

p180, lines 19-20

Spelling – instillation
Ocular effects – as reported. No additional comments.

p180, line 33 to p181, line 3

Important data concerning patch testing. No further comments.

3.3 p182, line 32 Genotoxicity, mention being in Table 3-9

No additional comments

p183 Table 3-9 – Genotoxicity

No additional comments

p185 Table 3-9 – Genotoxicity

No additional comments on CHO study

p188, line 15

No additional comments.

3.4 p189, lines 32-33 Toxicokinetics

No additional comment.

p190, lines 7-12

Handled appropriately for TOCP as being contained in the commercial mixtures of TCP.

p191, lines 18-22

Tough call on this one without the details. Appropriately handled.

p194, line 23 to p195, line 2

Would have been nice to have had testicular levels included. Otherwise, fine.

p196, lines 28-32

No additional comments.

p205, lines 1-13

No additional comments.

p206 Figure 3-12 – Proposed Metabolic Pathways
No additional comments.

p208, lines 9-25
No additional comments.

p210, lines 16-21
Important data to include. No additional comments.

3.5 p215, lines 1-10 Mechanism of Action
Difficult section to write. Conclusions appear appropriate especially the unknown statement about the role of metabolism. It was good to include.

p215, lines 21-25
No additional comments.

p217, line 18 to p218, line 31
Until more research is available both in animals and humans, the statements made about proposed mechanisms are quite appropriate.

p219, lines 9-10
no comment

p223, lines 21-26
No additional comments, quite remarkable lack of findings for specific terata.

p227, lines 19-22
No additional comments. Agree with speculation statement.

p231, line 33 to p232, line 3
Agree with statement and its emphasis about TOCP.

p233, lines 4-5
OK

p234, lines 7-9
OK

p236, lines 11-13
Comment: Most of the fertility decrease was in males. Having the next sentence that follows speak about the ovary, it appears fertility is referring to females only in first sentence.

p236, lines 32-34
ok

p237, lines 9-15
Data are rather limited for immunotox for TCP. Should there be a statement about extrapolating to humans may also be speculative at this time?
p237, line 17
Didn't this data question wether TCP or also its congeners (TOCP)?

p237, line 34 to p238, line 6
OK

4.0 Chemical and Physical Info

4.1	Identity	Overview, interesting background info	OK
4.2	p245, in Table 4-1	OK	
	p248, in Table 4-2	OK	

5.0 Production, Import. Use

5.1	p250, lines 11-13	OK
	p251, line 4	OK
	p252, in Table 5-1	OK
	p253, line 33	OK

Table 2, continued… TCP 'Discussions' in 2012 Profile

6.0 Potential for Human Exposure

6.3	p261, lines 28-31	OK
	p263, lines 19-21	OK
	p269, lines 6-8	OK
	p277, lines 8-10	OK
	p278, lines 21-24	ok

7.0 Analytical Methods

7.2	p285, in Table 7-2	OK

8.0 Regulations

p290 and pp295-6 Summary of all MRLs Appropriate

9.0 References

10.0 Glossary

Appendices **Appendix A Focus on these MRL Worksheets**

Reason *	Subs	MRL	MRL value (mg/kg/day)	Worksheet Page
Revised	TCEP	chronic	0.3 (2009) => 0.2 (2012)	A-8

COMMENTS: With limited data, best one can do. Acceptable.

Revised TnBP intermediate 0.02 (2009) => 0.08 (2012) A-18
COMMENTS: Most conservative. Acceptable.
Revised TnBP chronic 0.02 (2009) => 0.08 (2012) A-23
COMMENTS: Acceptable.
Revised TBEP intermediate 0.2 (2009) => 0.09 (2012) A-31
COMMENTS: Agree with analyses - Data quite consistent.

New TCP intermediate 0.04 (2012) A-48
COMMENTS: With the data set available the analyses is reasonable and appropriate. The big problem is the difference between the 3 month and 6 month ovarian findings (6/10 vs 1/10 at 7 mg/kg/day. All assessments are in the ball park. Agree.

New TCP chronic 0.02 (2012) A-53
COMMENTS: It is notable that for the 15month study for ovarian findings that 7/10 were noted but at two years 0/50 are found. However, the authors have performed the conservative analyses to assess risk for benchmark modeling. Excellent modeling work for all.
TYPO Table A-26 EXPSOED

* We ask you to closely review the Worksheets for the two totally new MRLs for TCP.
You should also review the Worksheets for the four MRLs that were revised from 2009.
No explicit review is needed for the Worksheets for the five MRLs that did not change from 2009.

< TP-PEFR-FINAL-Charge-To-Peer-Reviewers-2012-03-01.doc >

Table 3 'Selected MRL Rationale Statements' Document to be Reviewed

This table presents a listing of the page numbers in the 'Selected MRL Rationale Statements' document (that has been provided as an MS Word file) having all six MRLs to be reviewed in that document (four revised, two new).

Document Page	Substance and MRL	Status (2012)
2	TCEP chronic-duration COMMENTS: Acceptable	Revised
8	TnBP intermediate-duration COMMENTS: acceptable	Revised
15	TnBP chronic-duration COMMENTS: acceptable	Revised
18	TBEP intermediate-duration COMMENTS: acceptable	Revised
24	TCP intermediate-duration COMMENTS: acceptable	New
31	TCP chronic-duration COMMENTS: acceptable	New